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OXFORD HANDBOOK OF CARDIOLOGY

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Symbols and abbreviations

♂	male
♀	female
>	greater than
<	less than
≥	equal to or greater than
≤	equal to or less than
±	plus or minus
©	copyright
®	registered
™	trademark
~	approximately
↑	increased
↓	decreased
➲	cross-reference
🖱	website address
α	alpha
β	beta
δ	delta
γ	gamma
2Ch	two-chamber (view)
3Ch	three-chamber (view)
4Ch	four-chamber (view)
5Ch	five-chamber (view)
2D	two-dimensional
3D	three-dimensional
AAD	antiarrhythmic drug
ABG	arterial blood gas
ABPI	ankle–brachial pressure index
AC	attenuation correction
ACA	anomalous coronary artery
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACE2	angiotensin-converting enzyme 2
ACEi	angiotensin-converting enzyme inhibitor
ACHD	adult congenital heart disease
ACM	arrhythmogenic cardiomyopathy
ACR	albumin:creatinine ratio
ACS	acute coronary syndrome
ACT	activated clotting time
ACVD	atherosclerotic cardiovascular disease
AD	autosomal dominant; after-depolarization
ADA	adenosine deaminase
ADP	adenosine diphosphate
AED	automated external defibrillator
AF	atrial fibrillation
AFB	acid-fast bacilli
AFl	atrial flutter
AH	atrial–His
AHA	American Heart Association
AI	aortic insufficiency
AIDS	acquired immune deficiency syndrome
AKI	acute kidney injury
ALCAPA	anomalous left coronary artery from the pulmonary artery
ALP	alkaline phosphatase
ALS	advanced life support
ALT	alanine aminotransferase
ALVC	arrhythmogenic left ventricular cardiomyopathy
ANA	antinuclear antibodies
ANCA	antineutrophil cytoplasmic antibodies
AP	action potential; accessory pathway
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
APS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
AR	aortic regurgitation
ARB	angiotensin receptor blocker
ARCAPA	anomalous right coronary artery from the pulmonary artery
ARDS	acute respiratory distress syndrome
ARF	acute rheumatic fever; acute renal failure
ARNI	angiotensin receptor–neprilysin inhibitor

ARVC	arrhythmogenic right ventricular cardiomyopathy
AS	aortic stenosis; ankylosing spondylitis
ASD	atrial septal defect
AST	aspartate transaminase
AT	atrial tachycardia
ATP	adenosine triphosphate; anti-tachycardia pacing
AuD	autosomal dominant
AuR	autosomal recessive
AV	atrioventricular
AVN	atrioventricular node
AVNERP	atrioventricular node effective refractory period
AVNRT	atrioventricular node re-entrant tachycardia
AVR	aortic valve replacement
AVRT	atrioventricular re-entrant tachycardia
AVSD	atrioventricular septal defect
BBB	bundle branch block
BBV	bloodborne virus
BCNIE	blood culture-negative infective endocarditis
BCT	broad complex tachycardia
bd	twice daily
BiPAP	bilevel positive airway pressure
biVAD	biventricular assist device
BLS	basic life support
BMD	Becker muscular dystrophy
BMI	body mass index
BMS	bare metal stent
BNP	B-type natriuretic peptide
BP	blood pressure
BrS	Brugada syndrome
BSA	body surface area
BT	Blalock–Taussig
BTC	bridge to candidacy
BTT	bridge to transplantation
BVS	bioresorbable vascular scaffold
Ca2+	calcium ion
CABG	coronary artery bypass graft
CAC	coronary artery calcium
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
CCB	calcium channel blocker
CCF	congestive cardiac failure
CCP	cyclic citrullinated peptide
CCS	chronic coronary syndromes
CCTA	coronary computed coronary angiography
ccTGA	congenitally corrected transposition of the great arteries
CCU	coronary care unit
CEA	carcinoembryonic antigen
CETP	cholesterol ester transfer protein
CFAE	complex and fractionated atrial electrogram
CFR	coronary flow reserve
CHB	complete heart block
CHD	congenital heart disease
CK	creatinine/creatine kinase
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cl−	chloride ion
CMR	cardiac magnetic resonance
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CNS	central nervous system
CO	cardiac output
CO2	carbon dioxide
CoA	coarctation of the aorta
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
COX	cyclo-oxygenase
COX-1	cyclo-oxygenase 1
COX-2	cyclo-oxygenase 2
CPAP	continuous positive airways pressure
CPET	cardiopulmonary exercise testing
CPR	cardiopulmonary resuscitation
CPVT	catecholaminergic polymorphic ventricular tachycardia
CrCl	creatinine clearance
CRP	C-reactive protein
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy defibrillator
CRT-P	cardiac resynchronization therapy pacemaker
CS	coronary sinus
CT	computed tomography

CTCA	computed tomography coronary angiography
CTD	connective tissue disease
CTO	chronic total occlusion
CTPA	computed tomography pulmonary angiography
CV	cardiovascular
CVA	cerebrovascular accident
CVD	cardiovascular disease
CVP	central venous pressure
CW	continuous-wave (Doppler)
CXR	chest X-ray
DAPT	dual antiplatelet therapy
DBP	diastolic blood pressure
DCCV	direct current cardioversion
DCM	dilated cardiomyopathy
DEB	drug-eluting balloon
DES	drug-eluting stent
DFT	defibrillation threshold testing
DHP	dihydropyridine
DM	diabetes mellitus; dermatomyositis
DMARD	disease-modifying anti-rheumatic drug
DMD	Duchenne muscular dystrophy
DOAC	direct oral anticoagulant
DPD	3,3-diphosphono-1,2-propanodicarboxylic acid
dsDNA	double-stranded DNA
DSE	dobutamine stress echocardiography
DT	deceleration time
DTS	Duke Treadmill Score
DVT	deep vein thrombosis
EBV	Epstein–Barr virus
ECG	electrocardiography/m
ECLS	extracorporeal life support
ECMO	extracorporeal membrane oxygenation
ECV	extracellular volume
ED	erectile dysfunction
EDMD	Emery–Dreifuss muscular dystrophy
EDS	Ehlers–Danlos syndrome
EEG	electroencephalography
EF	ejection fraction
EGE	early gadolinium enhancement
eGFR	estimated glomerular filtration rate
EGPA	eosinophilic granulomatosis with polyangiitis
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
EMB	endomyocardial biopsy
EMD	electromechanical dissociation
EMF	endomyocardial fibrosis
EMG	electromyography
ENA	extractable nuclear antigen
ENT	ear, nose, and throat
EOA	effective orifice area
EOL	end of life
EP	electrophysiology
ERI	elective replacement indicator
ERNV	equilibrium radionuclide ventriculography
EROA	effective regurgitant orifice area
ERP	effective refractory period
ESC	European Society of Cardiology
ESM	ejection systolic murmur
ESR	erythrocyte sedimentation rate
ESRF	end-stage renal failure
ET	endotracheal
5-FU	5-fluorouracil
FAC	fractional area change
FAT	focal atrial tachycardia
FBC	full blood count
FCH	familial combined hyperlipidaemia
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FFP	fresh frozen plasma
FFR	fractional flow reserve
FH	familial hypercholesterolaemia
FiO2	fraction of inspired oxygen
Fr	French
FS	fractional shortening
FSH	facioscapulohumeral muscular dystrophy
GBCA	gadolinium-based contrast agent
GCA	giant cell arteritis
GFR	glomerular filtration rate
GGT	γ-glutamyl transpeptidase
GH	growth hormone
GI	gastrointestinal

GLP1-RA	glucagon-like peptide-1 receptor agonist
GLS	global longitudinal strain
GORD	gastro-oesophageal reflux disease
GP	general practitioner; glycoprotein
GPA	granulomatosis with polyangiitis
GTN	glyceryl trinitrate
h	hour
Hb	haemoglobin
HbA1c	glycated haemoglobin
HBIG	hepatitis B immunoglobulin
HBV	hepatitis B virus
HCM	hypertrophic cardiomyopathy
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDU	high dependency unit
HER2	human epidermal growth factor receptor 2
HERS	Heart and Estrogen/progestin Replacement Study
HF	heart failure
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HHV	human herpesvirus
HHV8	human herpesvirus 8
HIF	hypoxia inducible factor
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HMG-CoA	hydroxymethylglutaryl coenzyme A
HOCM	hypertrophic obstructive cardiomyopathy
HoHF	homozygous familial hypercholesterolaemia
HPV	human papillomavirus
HR	heart rate
HRA	high right atrium
HRS	Heart Rhythm Society
HRT	hormone replacement therapy
HS1	first heart sound
HS2	second heart sound
HSV	herpes simplex virus
HSVPB	His synchronous ventricular premature beat
HV	His–ventricle
IABP	intra-aortic balloon pump
IAS	interatrial septum
ICC	inherited cardiac condition
ICD	implantable cardioverter–defibrillator
ICegram	intracardiac electrogram
ICS	intercostal space
ICU	intensive care unit
IE	infective endocarditis
If	funny current; funny channel
IFG	impaired fasting glucose
IFNγ	interferon-γ
iFR	instantaneous wave-free ratio
IgA	immunoglobulin A
IgG	immunoglobulin G
IgG4	immunoglobulin G4
IGT	impaired glucose tolerance
IHD	ischaemic heart disease
IJV	internal jugular vein
IL	interleukin
ILR	implantable loop recorder
IM	intramuscularly
INOCA	ischaemia with non-obstructed coronary arteries
INR	international normalized ratio
IONA	Impact of Nicorandil in Angina
IR(ME)R	Ionizing Radiation Medical Exposure Regulations
ISDN	isosorbide dinitrate
ISMN	isosorbide mononitrate
ISR	in-stent restenosis
IV	intravenous
IVC	inferior vena cava
IVIg	intravenous immunoglobulin
IVRT	isovolumetric relaxation time
IVS	interventricular septum
IVUS	intravascular ultrasound
JAK	Janus kinase
JL	Judkins Left
JLNS	Jervell–Lange–Nielsen syndrome
JR	Judkins Right
JVP	jugular venous pressure
K+	potassium ion
KCl	potassium chloride
KD	Kawasaki disease
KDIGO	Kidney Disease Improving Global Outcomes

LA	left atrial/atrium
LAA	left atrial appendage
LAD	left axis deviation; left anterior descending
LAE	left atrial enlargement
LAMP	lysosomal-associated membrane protein 2
LAN	long-acting nitrate
LAO	left anterior oblique
LAX	long axis (view)
LBBB	left bundle branch block
LCA	left coronary artery
LCB	left coronary bypass
LCx	left circumflex
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LGE	late gadolinium enhancement
LGMD	limb-girdle muscular dystrophy
LIJ	left internal jugular
LIMA	left internal mammary artery
LMA	laryngeal mask airway
LMS	left main stem
LMWH	low-molecular weight heparin
LQTS	long QT syndrome
LSD	lysosomal storage disorder
LSE	left sternal edge
LV	left ventricular
LVAD	left ventricular assist device
LVEDD	left ventricular end-diastolic diameter
LVEDP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
LVF	left ventricular failure
LVH	left ventricular hypertrophy
LVMI	left ventricular mass index
LVNC	left ventricular non-compaction
LVOT	left ventricular outflow tract
LVOTO	left ventricular outflow tract obstruction
LVPWT	left ventricular posterior wall thickness
LVWT	left ventricular wall thickness
MACE	major adverse cardiac events

MAP	mean arterial pressure
MAPCA	Major aortopulmonary collateral artery
MAPK	mitogen-activated protein kinase
MCS	mechanical circulatory support
MCTD	mixed connective tissue disease
MCV	mean corpuscular volume
MD	myotonic dystrophy; muscular dystrophy
MD1	myotonic dystrophy 1
MD2	myotonic dystrophy 2
MDRD	Modification of Diet in Renal Disease
MDT	multidisciplinary team
MELAS	mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke
MERRF	myoclonic epilepsy with ragged red fibres
Mg2+	magnesium ion
MI	myocardial infarction
MIC	minimum inhibitory concentration
min	minute
MINOCA	myocardial infarction with non-obstructed coronary arteries
MMP	matrix metalloproteinase
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MPS	myocardial perfusion scintigraphy
MR	mitral regurgitation; magnetic resonance; modified release
MRA	mineralocorticoid receptor antagonist; magnetic resonance angiography
MRI	magnetic resonance imaging
MRSA	meticillin-resistant Staphylococcus aureus
MS	mitral stenosis
MV	mitral valve
MVD	multivessel coronary artery disease
MVP	mitral valve prolapse
mWHO	modified World Health Organization
Na+	sodium ion
NBM	nil by mouth

NBTV	non-bacterial thrombotic vegetation
NCT	narrow complex tachycardia
NICE	National Institute for Health and Care Excellence
NIV	non-invasive ventilation
NNT	number needed to treat
N2O	nitrous oxide
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug
NSF	nephrogenic systemic fibrosis
NSTEMI	non-ST-segment elevation myocardial infarction
NSVT	non-sustained ventricular tachycardia
NT-proBNP	N-terminal pro-BNP
NYHA	New York Heart Association
OCP	oral contraceptive pill
OCT	optical coherence tomography
od	once daily
OGTT	oral glucose tolerance test
OMT	optimal medical therapy
OOHCA	out-of-hospital cardiac arrest
OS	opening snap
PA	pulmonary artery
PaCO2	partial pressure of carbon dioxide in arterial blood
PAD	peripheral arterial disease
PAH	pulmonary arterial hypertension
PAN	polyarteritis nodosa
PaO2	partial pressure of oxygen in arterial blood
PAP	pulmonary artery pressure
PAPVD	partial anomalous pulmonary venous drainage
PASP	pulmonary arterial systolic pressure
PCI	percutaneous coronary intervention
PCR	polymerase chain reaction
PCSK9	proprotein convertase subtilisin/kexin type 9
PCWP	pulmonary capillary wedge pressure
PDA	patent ductus arteriosus
PDE-5	phosphodiesterase type 5
PDGF	platelet-derived growth factor
PE	pulmonary embolism
PEA	pulseless electrical activity
PEEP	positive end-expiratory pressure
PEP	post-exposure prophylaxis
PESI	Pulmonary Embolism Severity Index
PET	positron emission tomography
PFO	patent foramen ovale
PHT	pulmonary hypertension
PISA	proximal isovelocity surface area
PLAX	parasternal long-axis (view)
PM	polymyositis
PMC	percutaneous mitral commissurotomy
PMT	photomultiplier tube
PND	paroxysmal nocturnal dyspnoea
PO	orally (per os)
PO42−	phosphate
POBA	plain old balloon angioplasty
POTS	postural orthostatic tachycardia syndrome
PPAR	peroxisome proliferator-activated receptor
PPCI	primary percutaneous coronary intervention
PPCM	peripartum cardiomyopathy
PPI	proton pump inhibitor
PPM	permanent pacemaker
PR	pulmonary regurgitation
PR3	proteinase 3
PRF	pulse repetition frequency
PS	pulmonary stenosis
PSAX	parasternal short axis (view)
PSM	presystolic murmur
PT	prothrombin time
PTH	parathyroid hormone
PTLD	post-transplant lymphoproliferative disease
PTP	pre-test probability
PUO	pyrexia of unknown origin
PV	pulmonary valve
PVARP	post-ventricular atrial refractory period
PVD	peripheral vascular disease
PVE	prosthetic valve endocarditis; premature ventricular ectopic
PVR	pulmonary valve replacement; pulmonary vascular resistance
pVT	pulseless ventricular tachycardia

PW	pulsed-wave (Doppler)
PWT	posterior wall thickness
qd	once daily
qds	four times daily
RA	right atrium/atrial; rheumatoid arthritis
RAA	renin–angiotensin–aldosterone
RAAS	renin–angiotensin–aldosterone system
RAD	right axis deviation
RAE	right atrial enlargement
RAO	right anterior oblique
RBBB	right bundle branch block
RCA	right coronary artery
RCM	restrictive cardiomyopathy
RF	rheumatoid factor; radiofrequency
RFA	radiofrequency ablation
RHD	rheumatic heart disease
RIJ	right internal jugular
RIMA	right internal mammary artery
ROI	region of interest
ROS	reactive oxygen species
ROSC	return of spontaneous circulation
RR	respiratory rate
rtPA	recombinant tissue plasminogen activator
RV	right ventricle/ventricular
RVA	right ventricular apex
RVAD	right ventricular assist device
RVEDP	right ventricular end-diastolic pressure
RVH	right ventricular hypertrophy
RVOT	right ventricular outflow tract
RWMA	regional wall motion abnormality
RWS	Romano–Ward syndrome
RWT	relative wall thickness
SADS	sudden arrhythmic death syndrome
SAM	systolic anterior motion
SAN	sinoatrial node
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAVR	surgical aortic valve replacement
SAX	short-axis view
SBE	subacute bacterial endocarditis
SBP	systolic blood pressure
s/c	subcutaneously
SCD	sudden cardiac death
SCM	sternocleidomastoid muscle
SCORE2	Systematic Coronary Risk Evaluation 2
SCORE2-OP	Systematic Coronary Risk Evaluation 2 for older people
SCV	subclavian vein
SGA	supraglottic airway
SGLT2	sodium–glucose cotransporter 2
SHBG	sex hormone-binding globulin
S-ICD	subcutaneous implantable cardioverter–defibrillator
siRNA	small interfering ribonucleic acid
S/L	sublingual
SLE	systemic lupus erythematosus
SNRT	sinus node re-entrant tachycardia
SNS	sympathetic nervous system
SPECT	single-photon emission computed tomography
sPESI	simplified PESI
SpO2	oxygen saturation
SQTS	short QT syndrome
SR	sinus rhythm; slow-release
SS	Sjögren’s syndrome
SSRI	selective serotonin reuptake inhibitor
STEMI	ST-segment elevation myocardial infarction
STIR	short tau inversion recovery
STS	Society of Thoracic Surgeons
SV	stroke volume
SVC	superior vena cava
SVD	structural valve degeneration
SVi	stroke volume index
SVT	supraventricular ventricular tachycardia
T	tesla
TAPSE	tricuspid annular plane systolic excursion
TAPVD	total anomalous pulmonary venous drainage
TAVI	transcatheter aortic valve implantation
TB	tuberculosis
TC	total cholesterol
TDI	tissue Doppler imaging
TdP	torsades de pointes

tds	three times daily
TEVAR	thoracic endovascular repair
TFT	thyroid function test
TG	triglyceride
TGA	transposition of the great arteries
Th1	T-helper cell type 1
TIA	transient ischaemic attack
TID	transient ischaemic dilatation
TIMI	Thrombolysis in Myocardial Infarction
TKI	tyrosine kinase inhibitor
TLR	target lesion revascularization
TNF	tumour necrosis factor
TOD	target organ damage
TOE	transoesophageal echocardiography
ToF	tetralogy of Fallot
TPG	transpulmonary gradient
TR	tricuspid regurgitant/ regurgitation
TRL	triglyceride-rich lipoprotein
TS	tricuspid stenosis
TTE	transthoracic echocardiography
TTR	time in therapeutic range
TV	tricuspid valve
TWI	T wave inversion
UA	unstable angina
UACR	urine albumin:creatinine ratio
U&Es	urea and electrolytes
UFH	unfractionated heparin
ULN	upper limit of normal
US	ultrasound
VA	venoarterial; ventriculo-arterial
VAD	ventricular assist device
VBG	venous blood gas
VC	vena contracta
VEGF	vascular endothelial growth factor
VERP	ventricular effective refractory period
VF	ventricular fibrillation
VHD	valvular heart disease
VKA	vitamin K antagonist
VLDL	very low-density lipoprotein
VPB	ventricular premature beat
V/Q	ventilation/perfusion
VSD	ventricular septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
VTI	velocity time integral
VV	venovenous
vW	von Willebrand
VZV	varicella-zoster virus
WBC	white blood cell
WCC	white cell count
WCL	Wenckebach cycle length
WPW	Wolff–Parkinson–White (syndrome)
WU	Woods unit

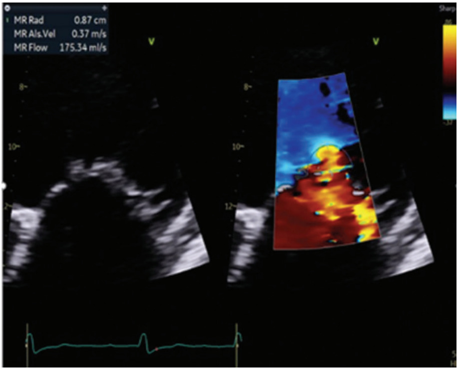
MR Rad 0.87 cm
MR Als.Vel 0.37 m/s
MR Flow 175.34 ml/s
V
V
8
10
12
8
10
12

Fig. 12.22 Measurement of PISA in mitral regurgitation.

Image courtesy of Paulo Bulleros.

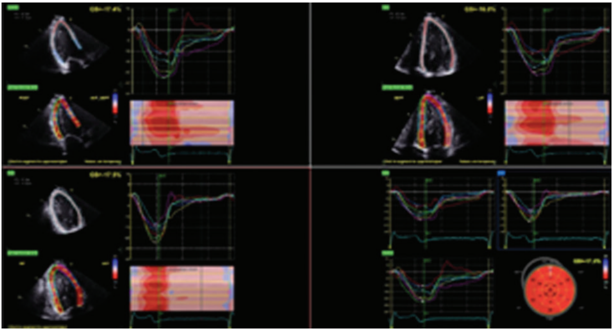

Fig. 12.23 Longitudinal strain measurement by using regions of interest.

Image courtesy of Paulo Bulleros.

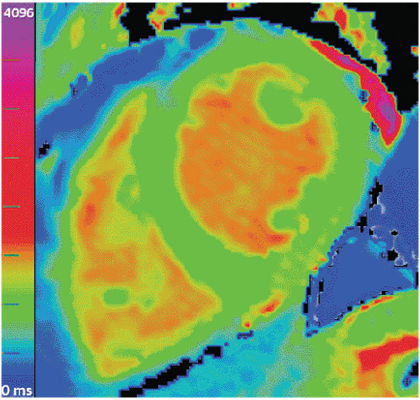

Fig. 12.32 An example of a good-quality native T1-map.

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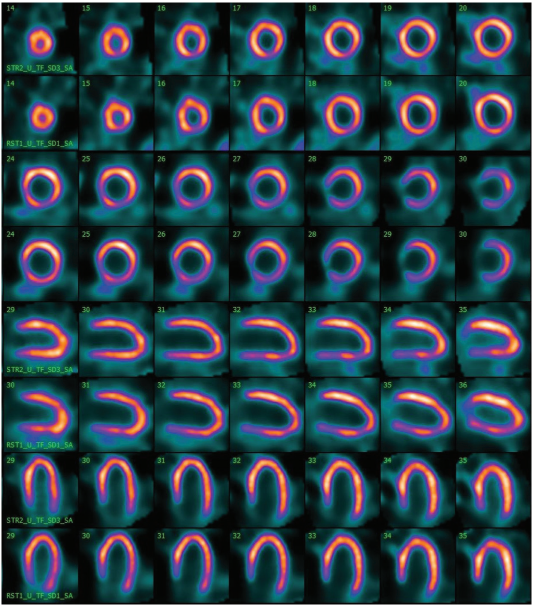
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14 15 16 17 18 19 20
RST1_U_TF_SD1_SA
24 25 26 27 28 29 30
24 25 26 27 28 29 30
29 30 31 32 33 34 35
STR2_U_TF_SD3_SA
30 31 32 33 34 35 36
RST1_U_TF_SD1_SA
29 30 31 32 33 34 35
STR2_U_TF_SD3_SA
29 30 31 32 33 34 35
RST1_U_TF_SD1_SA

Fig. 12.34 Normal myocardial perfusion scan using ^{99m}Tc-tetrofosmin. Stress images are positioned above the rest images. No perfusion mismatch is identified between stress and rest images. Top four rows represent the short-axis images. The next two rows represent the anterior, apical, and inferior walls. The final two rows represent the septum, and apical and lateral walls.

Image courtesy of Dr Nik Sabharwal.

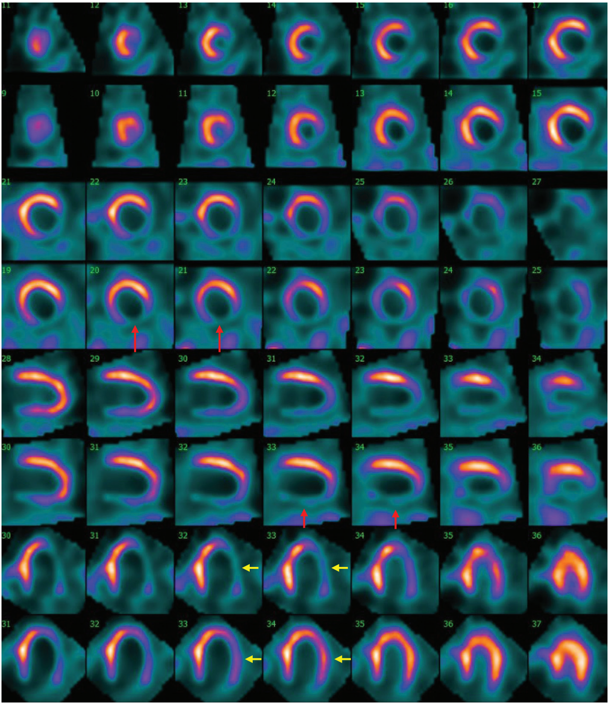

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Fig. 12.35 Abnormal MPS scan (isotope: ^{99m}Tc-tetrosfosmin). Stress images above the resting images. Inferior hypoperfusion at rest confirming infarction (red arrow). Lateral wall perfusion mismatch between rest and stress confirming a large volume of ischaemia (yellow arrow). RV prominence on stress scan is an adverse prognostic feature.

Image courtesy of Dr Nik Sabharwal.

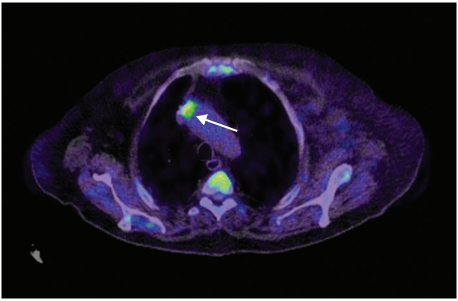

Fig. 12.36 Axial FDG-PET image. FDG avid uptake on the pacing lead in the superior vena cava at the level of the aortic arch.

Image courtesy of Dr Nik Sabharwal.

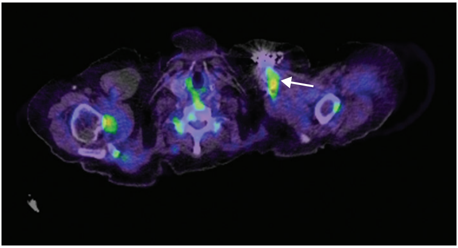

Fig. 12.37 Axial slice with FDG-avid area inferior to the implanted pacing device on the left.

Image courtesy of Dr Nik Sabharwal.

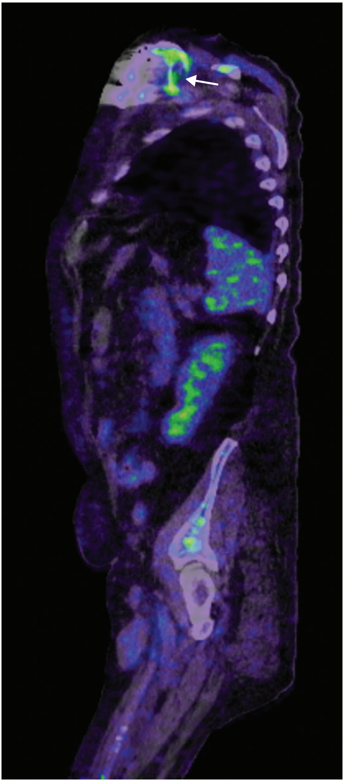

Fig. 12.38 Sagittal slice with FDG-avid area posterior to the implanted pacing device.

Image courtesy of Dr Nik Sabharwal.

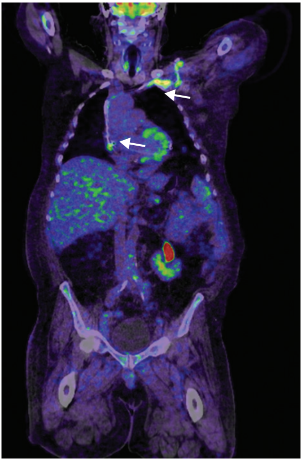

Fig. 12.39 Coronal slice with high FDG uptake over the pacing lead in the left subclavian area and tracking into the tissues towards the position of the pacing box (not seen). There is a further FDG-avid area overlying the lead in the right atrium near the tricuspid valve position. Non-specific cardiac uptake is identified.

Image courtesy of Dr Nik Sabharwal.

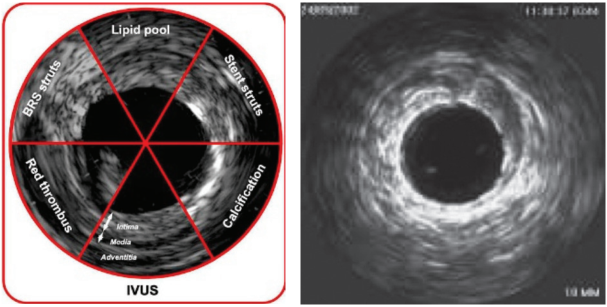
Lipid pool
BRS struts
Stent struts
Red thrombus
Calcification
Intima
Media
Adventitia
IVUS

Fig. 13.9 (a) Example of image obtained by intravenous ultrasound (IVUS). (b) IVUS image of a coronary stent (right).

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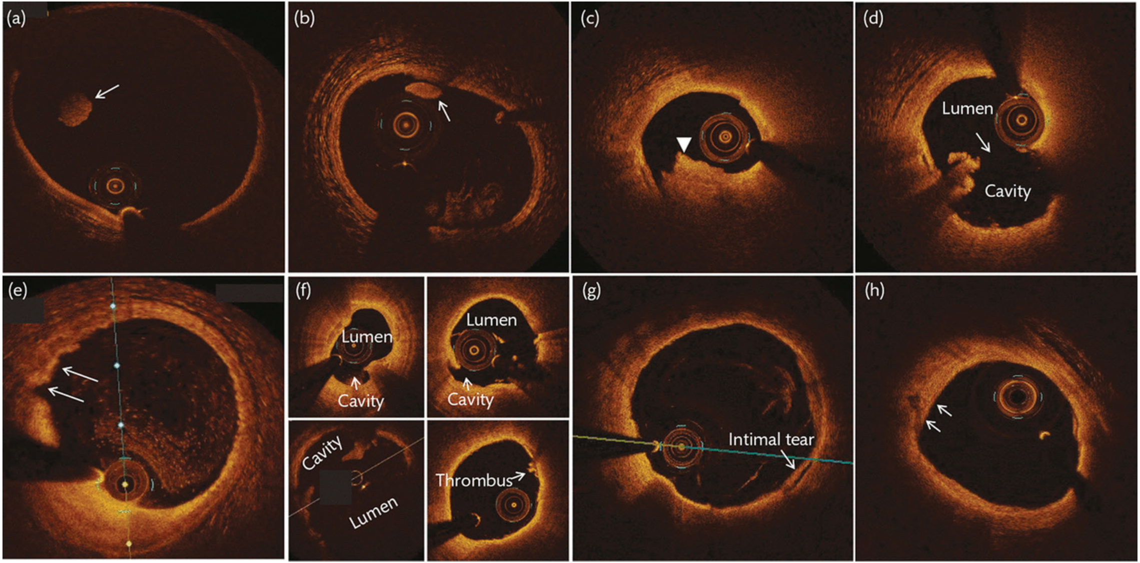

(a)
(b)
(c)
(d)
Lumen
Cavity
(e)
(f)
Lumen
Cavity
Lumen
Cavity
Cavity
Lumen
Thrombus
(g)
Intimal tear
(h)

Fig. 13.10 Optical coherence tomography images. (a) Red thrombus; (b) white thrombus; (c, d) plaque rupture; (e) plaque erosion; (f, g) ruptured caps, cavity, thrombus, and intimal tear; (h) friable tissue in the saphenous vein graft.

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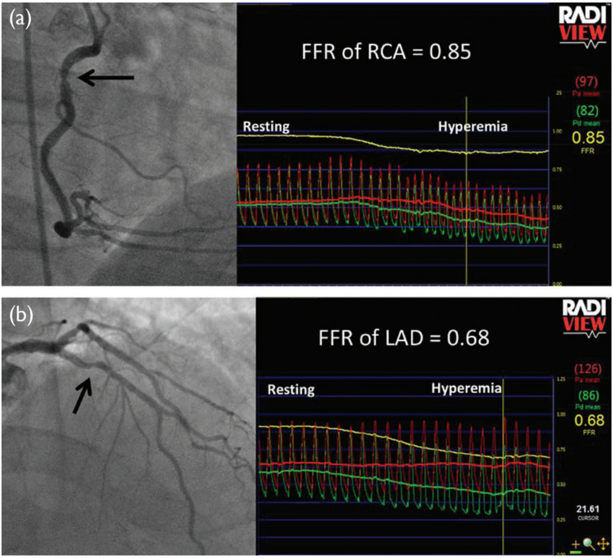
(a)
FFR of RCA = 0.85
RADI VIEW
(97)
Pa mean
(82)
Pd mean
0.85
FFR
Resting
Hyperemia
25
1.00
0.75
0.50
0.25
0.00
(b)
FFR of LAD = 0.68
RADI VIEW
(126)
Pa mean
(86)
Pd mean
0.68
FFR
Resting
Hyperemia
1.25
1.00
0.75
0.50
0.25
0.00
21.61
CURSOR

Fig. 13.12 Examples of coronary angiograms, with associated intracoronary flow assessments by FFR.

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Chapter 1

Coronary artery disease

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Pathophysiology of atherosclerosis

Overview

- Atherosclerosis is a disease of large and medium-sized arteries.
- Derived from Latin hardening ('sclerosis') of the arteries ('athero').
- Characterized by a gradual build-up of fatty plaques within the arterial wall, which eventually results in a significant narrowing of the vessel lumen, impairing blood flow to distal tissues.
- These plaques may also cause acute coronary syndromes (ACS) by becoming unstable and triggering coronary thrombosis.

Pathophysiology

The development of atherosclerosis is a progressive process.

Fatty streak development

- This can begin in as early as childhood and early adolescence.
- Low-density lipoprotein (LDL) cholesterol particles enter the intima of the coronary arteries where they undergo oxidation into proinflammatory particles, which provoke an inflammatory response.
- Endothelial cells also secrete cytokines and chemokines that attract and activate these inflammatory cells. They additionally secrete large amounts of growth factors such as platelet-derived growth factor (PDGF). This promotes vascular smooth muscle cell proliferation and extracellular matrix deposition.
- Monocytes are activated to become macrophages. Macrophages act as local 'scavenger' cells, with the capacity to take up LDL cholesterol, ultimately becoming the characteristic 'foam cells' of established atherosclerosis. Due to the nature of 'foam cells', they are unable to readily leave the intima of the vessel.

Early fibroatheroma

- In a bid to remove abnormal lipids, foam cells recruit proinflammatory cells such as T-helper cell type 1 (Th1) lymphocytes, which, in turn, secrete interferon-γ (IFNγ) and interleukin (IL) 2 (IL-2), which stimulate monocytes to become inflammatory macrophages.
- These macrophages secrete large amounts of reactive oxygen species (ROS) and extracellular enzymes, including matrix metalloproteinases (MMPs) (degrade extracellular matrix proteins) and myeloperoxidase (MPO) (pro-oxidative and proinflammatory).
- Consequently, more foam cells form and more cytokines, proteases, and ROS are expressed. These cytokines drive smooth muscle cell and fibroblast proliferation, and also promote endothelial activation. The ROS oxidize LDL, further driving its uptake by macrophages, thus creating a positive feedback loop.

Fibrous plaques

- The key step in the transition from fatty streak to plaque is extracellular lipid accumulation. Lipids accumulate between smooth muscle cells and gradually coalesce to form large lipid pools.
- This also contains dead foam cells and macrophages, and is therefore referred to as the necrotic lipid core.
- Fibroblasts enter the plaque and secrete collagen, causing fibrosis.
- The necrotic lipid core and surrounding fibrosis thus form the fibroatheroma. The core may, with time, become covered by a thick, fibrous cap.

Advanced atheroma

- Further plaque growth initially causes outward vessel wall remodelling, reducing the lumen size and the vessel's ability to deliver blood.
- Progressive plaque accumulation results in luminal narrowing and ultimately vessel obstruction.
- Erosion or denudation of the endothelial layer, or rupture of the overlying fibrous cap of the plaque, may expose the highly thrombogenic lipid-rich core of the plaque to circulating blood.
- This leads to acute thrombosis, which may rapidly occlude the vessel.
- Several studies have shown that a large proportion of myocardial infarctions (MI)s are caused by acute destabilization of plaques that were previously not obstructing flow in the vessel, suggesting that the likelihood of an acute coronary event is more closely related to the stability of the plaque rather than to the severity of the stenosis.
- Fig. 1.1 demonstrates the stepwise process of atheroma formation.

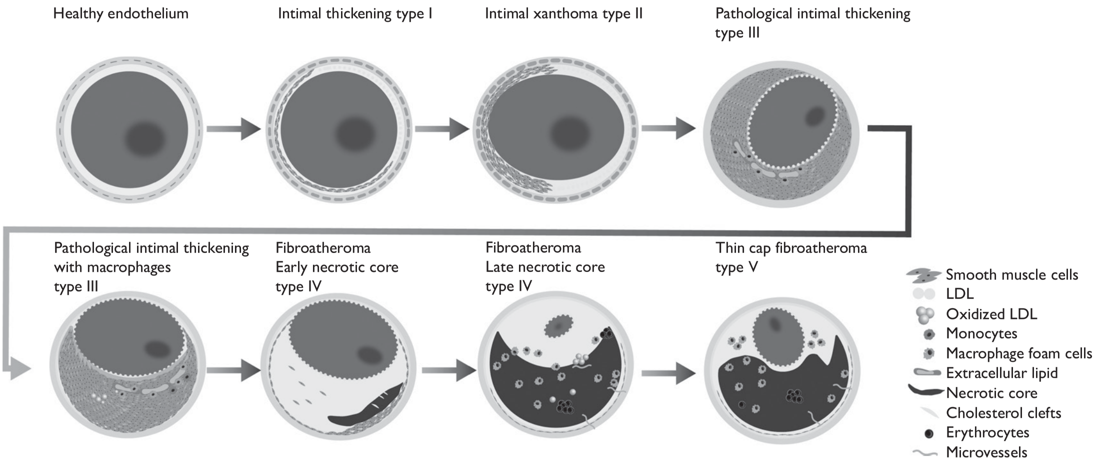

Healthy endothelium
Intimal thickening type I
Intimal xanthoma type II
Pathological intimal thickening type III
Pathological intimal thickening with macrophages type III
Fibroatheroma Early necrotic core type IV
Fibroatheroma Late necrotic core type IV
Thin cap fibroatheroma type V
Smooth muscle cells
LDL
Oxidized LDL
Monocytes
Macrophage foam cells
Extracellular lipid
Necrotic core
Cholesterol clefts
Erythrocytes
Microvessels

Fig. 1.1 Pathogenesis of atherosclerosis.

Illustrator: Drew Provan.

Cardiovascular disease: epidemiology

- Cardiovascular disease (CVD) is the most common cause of death in Europe, accounting for >4 million deaths per year.
- Coronary artery disease (CAD) accounts for 1.8 million deaths.
- CVD also represents a significant economic burden. In 2009, 9% of health expenditure in Europe was directed towards those with CVD.
- CVD is declining, with a reduction of almost 50% in some countries, largely due to the effect of preventative measures.
- It is important to note that important risk factors remain. While cholesterol and smoking rates are ↓, obesity and diabetes mellitus (DM) are ↑.

Coronary artery disease: risk factors

- Risk factors in men and women are largely similar (see Table 1.1).
- However, some risk factors tend to confer a higher risk in women (smoking, DM, and higher triglyceride (TG) levels).

Table 1.1 Modifiable and non-modifiable risk factors for coronary artery disease

Non-modifiable risk factors	Modifiable risk factors
Age	Smoking
♂ sex	Obesity
Family history	Psychological stress
Ethnic origin	Diabetes mellitus
	Dyslipidaemia
	Hypertension
	Inflammatory conditions

Age

- The UK population is ageing; 18% are currently aged ≥65 years, and 2.4% ≥85 years. These numbers are set to ↑.
- Ageing is a major risk factor for atherosclerotic disease, due to the degenerative process associated with ageing per se, together with the cumulative impact of risk factors with ↑ age.

Gender and hormone replacement therapy

- CAD is more common in men than in women, and the onset tends to be earlier in men. However, the incidence of CAD in women ↑ rapidly at menopause, and once >65 years, it is similar to that in men.
- It has been postulated that ♀ sex hormones contribute to the lower risk of atherosclerotic disease in premenopausal women.
- However, several large randomized controlled trials of hormone replacement therapy (HRT) in post-menopausal women with and without atherosclerosis (e.g. Women's Health Initiative, Heart and Estrogen/progestin Replacement Study (HERS)/HERS II, ESPRIT) have shown that HRT does not reduce the risk of cardiovascular (CV) events.
- HRT may, in fact, lead to a small, but significant, ↑ in morbidity and mortality from CVD and other diseases. Therefore, HRT is not recommended for prevention of atherosclerotic disease.

Family history of atherosclerotic disease

- CAD is a multifactorial disorder, caused by interactions between lifestyle, the environment, and the effects of multiple genetic variations.
- Family history is significant when CVD presents in a first-degree ♂ relative aged <55 years or in a ♀ relative aged <65 years.
- Genetic screening for those at ↑ CAD risk is not routine but may be used in some cases (e.g. familial hypercholesterolaemia (FH)).

Ethnic and geographical origin

Ethnicity is an important risk factor for CAD. For example, South Asians (Indian subcontinent) and sub-Saharan Africans have an ↑ incidence, compared with other ethnicities. The European Society of Cardiology (ESC)[1] has classified countries into areas of risk (see Table 1.2).

Table 1.2 Countries grouped by risk of cardiovascular disease

Very high risk	High risk	Moderate risk	Low risk
Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Montenegro, Morocco, Republic of Moldova, Romania, Russian Federation, Serbia, Syria, Macedonia, Tunisia, Ukraine, Uzbekistan	Albania, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Kazakhstan, Poland, Slovakia, Turkey	Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Portugal, San Marino, Slovenia, Sweden	Belgium, Denmark, France, Israel, Luxembourg, Norway, Spain, Switzerland, the Netherlands, UK

Smoking

- Smoking significantly ↑ the risk of CAD and is a major contributor to acute thrombotic events, as seen in young/middle-aged individuals who present with MI. Second-hand smoke can also ↑ the risk of CAD.
- Smoking cessation carries almost immediate benefit, and although the long-term benefits are ↑ in those who stop smoking aged <40 years, cessation later in life is also beneficial. For example, in those aged 30–59 years who stop smoking after an MI, the 5-year mortality is 10%, compared with 14% in those who continue to smoke.
- All individuals should be advised to stop smoking.
- Focused psychosocial support, nicotine replacement, and pharmacological therapy are effective in helping individuals to stop. These services are delivered in an integrated fashion by smoking cessation clinics.

Diabetes and hypertension

(See ➔ Diabetes mellitus: overview, pp. 16–7.)

- ↓ BP improves CVD risk (see ➔ Hypertension: overview, pp. 30–1).

Psychosocial factors

- The INTERHEART study demonstrated that various psychosocial factors ↑ the risk of MI. Psychosocial factors include low socioeconomic status (low education level, low-income job, living in a deprived area), stress, depression and anxiety, and other mental disorders, as well as lack of social support.

Obesity

- Obesity is associated with an ↑ risk of CVD.

Inflammatory conditions

- Systemic inflammatory conditions considerably ↑ CVD risk.
- Rheumatoid arthritis demonstrates a relative risk of 1.4 in men and 1.5 in women. Other conditions such as ankylosing spondylitis and psoriasis may also contribute to ↑ risk, but the evidence is less clear.

Reference

1. Vissere FLJ, Mach F, Smulders YM, *et al*.; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;**42**:3227–337.

CAD: risk stratification

Importance of risk stratification

- Identifying and treating risk factors are essential to preventing CVD.
- When multiple risk factors coexist, the CV risk is greatly ↑, suggesting a synergistic interaction between these factors.

Risk assessment tools

- All guidelines recommend calculation of an individual's CVD risk.
- The Systematic Coronary Risk Evaluation 2 (SCORE2) and SCORE2 for older people (aged ≥70 years) (SCORE2-OP) is recommended by the ESC[1] (see Fig. 1.2). This can be used to assess CVD risk in low-, moderate-, high-, and very high-risk countries, as defined by national CVD mortality rates (see Table 1.2).
- This calculates an individual's 10-year risk of fatal and non-fatal CV events. It is based on age, gender, blood pressure (BP), cholesterol, and smoking. The score calculates a percentage risk score.
- Individuals such as those with known CAD, DM, chronic kidney disease (CKD), FH, carotid/femoral plaques, coronary artery calcium (CAC) score >100, high levels of lipoprotein, or very high levels of individual risk factors are already considered high risk and do not need a risk score calculation.

Cardiovascular disease risk according to age

Given that advanced age is a risk factor for CVD, but managing risk factors over a lifetime is more beneficial in younger people, the risk thresholds when considering treatment are lower in the younger population (see Fig. 1.3).

Practicality of risk calculation

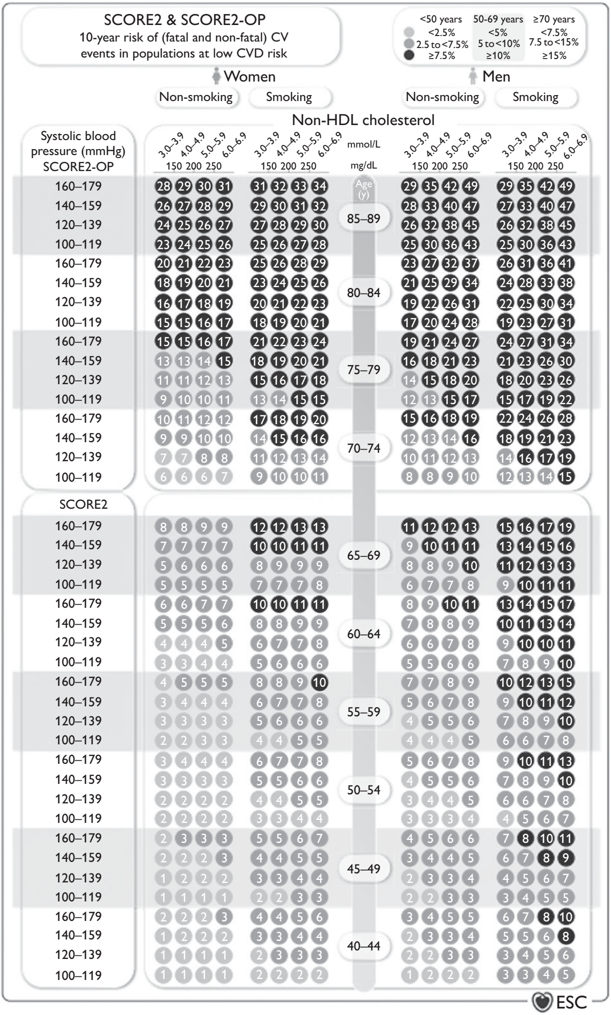
- The risk score is calculated by identifying the patient's gender, then their smoking status, and then their age. The colour of the cell approximating to the patient's systolic BP (SBP) and total cholesterol (TC) level then gives the overall risk score, depending on their age (pretreatment values should be used).
- Risk scores do not include all possible risk factors (see Box 1.1).

Box 1.1 Additional factors that may alter cardiovascular disease risk

- Obesity
- Inactivity
- Stress
- Psychiatric disorders
- Immune-mediated inflammatory disorders
- Family history of premature cardiovascular disease
- Social deprivation

Other scoring systems

- Other scoring systems that may be in use in clinical practice include the Framingham Risk Scoring system, QRISK, ASSIGN, PROCAM, pooled cohort equation, CUORE, Arriba, and Globorisk. These generally perform well in populations from which they were derived.



SCORE2 & SCORE2-OP
10-year risk of (fatal and non-fatal) CV events in populations at low CVD risk

	<50 years	50-69 years	≥70 years
●	<2.5%	<5%	<7.5%
●	2.5 to <7.5%	5 to <10%	7.5 to <15%
●	≥7.5%	≥10%	≥15%

Non-HDL cholesterol (mmol/L; mg/dL 150 200 250)

Age (y)	Systolic blood pressure (mmHg)	Women Non-smoking				Women Smoking				Men Non-smoking				Men Smoking			
		3.0–3.9	4.0–4.9	5.0–5.9	6.0–6.9	3.0–3.9	4.0–4.9	5.0–5.9	6.0–6.9	3.0–3.9	4.0–4.9	5.0–5.9	6.0–6.9	3.0–3.9	4.0–4.9	5.0–5.9	6.0–6.9
	SCORE2-OP																
85–89	160–179	28	29	30	31	31	32	33	34	29	35	42	49	29	35	42	49
	140–159	26	27	28	29	29	30	31	32	28	33	40	47	27	33	40	47
	120–139	24	25	26	27	27	28	29	30	26	32	38	45	26	32	38	45
	100–119	23	24	25	26	25	26	27	28	25	30	36	43	25	30	36	43
80–84	160–179	20	21	22	23	25	26	28	29	23	27	32	37	26	31	36	41
	140–159	18	19	20	21	23	24	25	26	21	25	29	34	24	28	33	38
	120–139	16	17	18	19	20	21	22	23	19	22	26	31	22	25	30	34
	100–119	15	15	16	17	18	19	20	21	17	20	24	28	19	23	27	31
75–79	160–179	15	15	16	17	21	22	23	24	19	21	24	27	24	27	31	34
	140–159	13	13	14	15	18	19	20	21	16	18	21	23	21	23	26	30
	120–139	11	11	12	13	15	16	17	18	14	15	18	20	18	20	23	26
	100–119	9	10	10	11	13	14	15	15	12	13	15	17	15	17	19	22
70–74	160–179	10	11	12	12	17	18	19	20	15	16	18	19	22	24	26	28
	140–159	9	9	10	10	14	15	16	16	12	13	14	16	18	19	21	23
	120–139	7	7	8	8	11	12	13	14	10	11	12	13	14	16	17	19
	100–119	6	6	6	7	9	10	10	11	8	8	9	10	12	13	14	15
	SCORE2																
65–69	160–179	8	8	9	9	12	12	13	13	11	12	12	13	15	16	17	19
	140–159	7	7	7	7	10	10	11	11	9	10	11	11	13	14	15	16
	120–139	5	6	6	6	8	9	9	9	8	8	9	10	11	12	13	13
	100–119	5	5	5	5	7	7	7	8	6	7	7	8	9	10	11	11
60–64	160–179	6	6	7	7	10	10	11	11	8	9	10	11	13	14	15	17
	140–159	5	5	5	6	8	8	9	9	7	8	8	9	10	11	13	14
	120–139	4	4	4	5	6	7	7	8	6	6	7	8	9	10	10	11
	100–119	3	3	4	4	5	6	6	6	5	5	6	6	7	8	9	10
55–59	160–179	4	5	5	5	8	8	9	10	7	7	8	9	10	12	13	15
	140–159	3	4	4	4	6	7	7	8	5	6	7	8	9	10	11	12
	120–139	3	3	3	3	5	6	6	6	4	5	5	6	7	8	9	10
	100–119	2	2	3	3	4	4	5	5	4	4	4	5	6	6	7	8
50–54	160–179	3	4	4	4	6	7	7	8	5	6	7	8	9	10	11	13
	140–159	3	3	3	3	5	5	6	6	4	5	5	6	7	8	9	10
	120–139	2	2	2	2	4	4	5	5	3	4	4	5	6	6	7	8
	100–119	2	2	2	2	3	3	4	4	3	3	3	4	4	5	6	7
45–49	160–179	2	3	3	3	5	5	6	7	4	5	6	6	7	8	10	11
	140–159	2	2	2	3	4	4	5	5	3	4	4	5	6	7	8	9
	120–139	1	2	2	2	3	3	4	4	2	3	3	4	4	5	6	7
	100–119	1	1	1	1	2	2	3	3	2	2	3	3	3	4	5	5
40–44	160–179	2	2	2	3	4	4	5	6	3	4	5	5	6	7	8	10
	140–159	1	2	2	2	3	3	4	4	2	3	3	4	5	5	6	8
	120–139	1	1	1	1	2	3	3	3	2	2	3	3	3	4	5	6
	100–119	1	1	1	1	2	2	2	2	1	2	2	2	3	3	4	5

ESC

Fig. 1.2 SCORE2 charts.

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	<50 years	**50–69 years**	**≥70 years***
Low-to-moderate CVD risk: risk factor treatment generally not recommended	<2.5%	<5%	<7.5%
High CVD risk: risk factor treatment should be considered	2.5 to <7.5%	5 to <10%	7.5 to <15%
Very high CVD risk: risk factor treatment generally recommended*	≥7.5%	≥10%	≥15%

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Fig. 1.3 Cardiovascular disease (CVD) risk categories according to age.

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Classification of risk

- In those with high- and very high-risk scores, aggressive risk factor management should be considered/recommended, respectively.
- Assessment of carotid/femoral plaque burden, as well as CAC score, should be considered in those at moderate risk, as a CAC score of >100 and plaque burden may suggest that the patient should be reclassified into a higher-risk category.

Reference

1. Vissere FLJ, Mach F, Smulders YM, *et al*.; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;**42**:3227–337.

CAD: risk factor modification

Behavioural changes and psychosocial factors

Cognitive behavioural therapies may be employed in order to support lifestyle changes. Addressing psychosocial factors may help to facilitate behavioural change.

Weight loss

Weight reduction improves BP, dyslipidaemia, and type II DM risk. May be achieved by combined diet improvement and ↑ physical activity.

Physical activity

- Adults should engage in 150min/week of moderate-intensity (brisk walking, slow cycling, doubles tennis, water aerobics) exercise or in 75min of vigorous-intensity (running, cycling >15km/h, swimming laps) exercise in addition to resistance exercise twice a week.
- ↑ physical activity can be facilitated by regular assessment/support.

Diet

- Some dietary changes have important CVD risk benefits (see Box 1.2).

Box 1.2 Dietary changes to reduce cardiovascular disease risk

- Replacement of saturated fats with polyunsaturated fatty acids
- ↓ in trans-unsaturated fatty acids
- 30–45g fibre/day (wholegrain)
- 2–3 servings of fruit/day (>200g)
- <5g salt/day
- 2–3 servings of vegetables/day (>200g)
- Oily fish 1–2 times/week
- 30g unsalted nuts
- Alcohol: ≤2 units/day for men and ≤1 unit/day for women

Lipid control

Reduction in LDL cholesterol level reduces CV events. Therefore, lipid-lowering agents are recommended if target LDL levels are not met (see ➔ Dyslipidaemias: guidelines and targets, p. 26).

Smoking cessation

- This is the most cost-effective strategy to prevent CVD.
- Smokers should be identified and provided with advice to stop.
- They should be supported and offered nicotine replacement (chewing gum, patches, sublingual (S/L) tablets) or therapies such as bupropion (antidepressant) and varenicline (partial nicotine receptor agonist).

Diabetes mellitus

Intensive management of hyperglycaemia and weight, as well as of concomitant hypertension and dyslipidaemias, is essential (see ➔ Diabetes mellitus: management in atherosclerotic cardiovascular disease, pp. 18–21).

Hypertension

BP reduction improves CVD risk (see ➔ Hypertension: investigations, p. 34; ➔ Hypertension: management, pp. 36–9).

Diabetes mellitus: overview

- The prevalence of DM worldwide continues to grow, affecting up to 10% of the population in countries such as China and India.
- In 2017, 60 million adults in Europe were estimated to have type II DM, with a predicted ↑ to over 600 million by 2045.
- DM leads to a 2-fold risk of CAD, as well as cerebrovascular accident (CVA) and vascular complications, irrespective of other risk factors. This risk is greatest in younger individuals and women, and particularly those with long-standing DM. Around 20–30% of those with CAD have DM.

Diagnosis

- A diagnosis of DM is confirmed if glycated haemoglobin (HbA1c) is ≥6.5% (>48mmol/L) or fasting plasma glucose concentration is ≥7mmol/L.
- Pre-DM includes impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).
- An oral glucose tolerance test (OGTT) is useful if fasting plasma glucose or HbA1c are inconclusive, or to diagnose IFG and IGT:
  - *DM:* blood sugar of ≥11.1mmol/L 2h post-OGTT.
  - *IFG:* fasting blood sugar of 5.6–6.9mmol/L and <7.8mmol/L 2h post-OGTT.
  - *IGT:* fasting blood sugar of <7mmol/L and 7.8–11.0mmol/L 2h post-OGTT.

(NB all values based on American Diabetes recommendations 2019.)

General management strategies

Weight loss

- Weight loss may prevent the development of type II DM.
- Weight loss of >5% may improve glycaemic control in those with established type II DM.

Physical activity

- The optimal weekly activity should include 150min of moderate-intensity activity or 75min of vigorous activity a week, in addition to resistance exercise twice a week.

Diet

- A Mediterranean diet, with addition of nuts and olive oil, ↓ CV events. Protein should only be ↓ in the event of kidney disease.

Blood pressure

- In those with DM, the main goal is to ↓ the SBP to 120–130mmHg. SBP lower than this does not ↓ CV events other than CVA. The diastolic BP (DBP) should be 70–80mmHg. In those aged >65 years, the systolic target should remain between 130 and 139mmHg.
- If the BP is >140 and/or >90mmHg, an angiotensin-converting enzyme inhibitor (ACEi) (particularly if there is evidence of albuminuria or proteinuria), or an angiotensin receptor blocker (ARB) if an ACEi is not tolerated, is preferred. A calcium channel blocker (CCB) or a thiazide diuretic may be added if targets are not achieved.

- The combination of a β-blocker and thiazide diuretics may promote the development of DM and should be avoided in those who are pre-DM. Carvedilol and nebivolol may be preferable due to their ability to improve insulin sensitivity.

Lipids

An LDL cholesterol reduction of 1mmol/L can lead to a 9% reduction in all-cause mortality and a 21% reduction in CV events (see ➔ Dyslipidaemias: guidelines and targets, p. 26).

Modification of other risk factors

- Combined reduction of risk factors has an additive effect with regard to CV risk. For general management of risk factors, see ➔ CAD: risk factor modification, pp. 14–15.

Glucose control

- Glucose control to near-normal HbA1c significantly ↓ microvascular complications. Benefits on macrovascular complications are seen when tight glucose control (HbA1c <7.0%/55mmol/mol) is initiated early in the disease course.
- Tight glucose control may not be suitable for all individuals, such as the elderly who may be more at risk from hypoglycaemic episodes, or those who are frail, with multiple comorbidities or limited life expectancy (aim for HbA1c <8.5%/69mmol/mol).
- Management of these individuals should be on a case-by-case basis, aiming for less stringent targets.

Glucose-lowering agents

There are five main groups of agents (see Table 1.3).

Table 1.3 Pharmacological agents for management of type II diabetes

Mechanism of action	Class	Examples
Insulin sensitizer	Biguanide	Metformin
	Thiazolidinediones	Pioglitazone
Insulin provider	Hormone	Insulin
Insulin secretagogue	Sulfonylurea	Gliclazide
Incretin-based agent	Dipeptidyl peptidase 4 inhibitors	Sitagliptin, linagliptin
	Glucagon-like peptide-1 receptor agonists	Liraglutide, semaglutide, dulaglutide
Gastrointestinal glucose absorption inhibitor	α-glucosidase inhibitor	Acarbose
Renal glucose reuptake inhibitor	Sodium–glucose cotransporter inhibitors	Empagliflozin, canaglifozin, dapagliflozin

DM: management in atherosclerotic cardiovascular disease

Glucose-lowering treatment in coronary artery disease

- In those without atherosclerotic CVD (ACVD) or severe target organ damage (TOD), CV risk is determined via SCORE2-Diabetes (see Fig. 1.4). This extends the use of the SCORE2 risk model to those with diabetes (aged 40–69 years).
- Generally, those medications with proven CV risk benefits should be prioritized in those with ACVD.

Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk ≥20% using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 10 to <20% using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 5 to <10% using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk <5% using SCORE2-Diabetes

Fig. 1.4 Classification of cardiovascular (CV) risk in patients with diabetes. Severe target organ damage (TOD): estimated glomerular filtration rate (eGFR) <45mL/min/1.73m² or eGFR 45–59mL/min/1.73 m² and microalbuminuria (urine albumin:creatinine ratio (UACR) 30–300mg); or proteinuria (UACR >300mg/g); or presence of microvascular disease in at least three different sites.

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The ESC guidelines are summarized in Fig. 1.5.[1]

Metformin

- In the UKPDS study of overweight/obese patients without CVD, metformin use demonstrated a 39% ↓ in MI and 50% ↓ in coronary-related death. As a result, metformin should be considered in type II DM with low/moderate CV risk (ESC Class IIa recommendation).
- Metformin can be considered in those without ACVD or severe TOD, but with high/very high CV risk (ESC Class IIb recommendation).

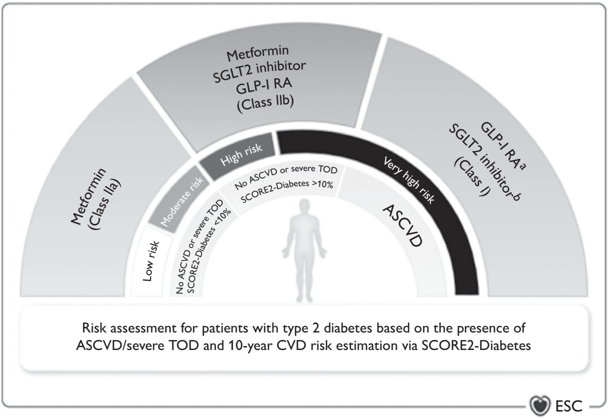
Metformin
(Class IIa)
Metformin
SGLT2 inhibitor
GLP-1 RA
(Class IIb)
GLP-1 RAa
SGLT2 inhibitorb
(Class I)
Low risk
Moderate risk
High risk
Very high risk
No ASCVD or severe TOD
SCORE2-Diabetes <10%
No ASCVD or severe TOD
SCORE2-Diabetes >10%
ASCVD
Risk assessment for patients with type 2 diabetes based on the presence of ASCVD/severe TOD and 10-year CVD risk estimation via SCORE2-Diabetes
ESC

Fig. 1.5 Algorithm for treatment of patients with type II diabetes.

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Glucagon-like peptide-1 receptor agonists

- Eight randomized trials have studied the CV effects of glucagon-like peptide-1 receptor agonists (GLP1-RAs) in those with, or at high risk of, CVD. Five of these studies demonstrated beneficial effects on the composite primary outcome of time to CV death, MI, and CVA, when compared with placebo. Pooled analyses also suggested a greater absolute risk reduction in those with established AVCD, compared with those without.
- Sodium–glucose cotransporter 2 (SGLT2) inhibitors should be given to those with ACVD and type II DM to ↓ CV risk, independent of glucose control and metformin use (ESC Class I recommendation), and may be considered in those without ACVD or severe TOD, but with high or very high CV risk (ESC Class IIb recommendation).

Sodium–glucose cotransporter 2 inhibitors

- A meta-analysis of six SGLT2 inhibitor trials showed a reduction in the composite primary end point of time to CV death, MI, or CVA. This effect was greatest in those with AVCD. Both dapagliflozin and empagliflozin also reduced heart failure (HF) hospitalizations.
- SGLT2 inhibitors should be given to those with ACVD and type II DM to ↓ CV risk, independent of glucose control and metformin use (ESC Class I recommendation), and may be considered in those without ACVD or severe TOD, but with high or very high CV risk (ESC Class IIb recommendation).

Thiazolidinediones

- Avoid in those with HF.

- The PROACTIVE trial showed ↑ HF with pioglitazone than with placebo.

Dipeptidyl peptidase 4 inhibitors

- Have not been shown to have any significant CV benefits.
- Should be avoided in those with type II DM and high risk of HF due to ↑ risk of HF hospitalization (SAVOR-TIMI) and ↑ HF events (EXAMINE).

Sulfonylureas

- Although more effective than lifestyle interventions, sulfonylureas are not as effective as metformin.
- Sulfonylureas are safe to use in CVD but have not demonstrated improvements in CV outcomes.

Insulin

- Should be prescribed in ACS with blood glucose >10mmol/L.

Antiplatelet agents

Secondary prevention

- Guidance for aspirin is the same in those with and without DM.
- There is a clear benefit of ticagrelor and prasugrel over clopidogrel with regard to dual antiplatelet therapy (DAPT).

Aspirin in primary prevention

- In those without a history of ACVD or revascularization, aspirin may be considered, in the absence of contraindications, to prevent a first severe vascular event (ESC Class IIb recommendation).

Coronary intervention

- In a subset of patients with DM in the BEST study, death, MI, or the need for target vessel revascularization was significantly ↑ in those who underwent percutaneous coronary intervention (PCI) vs coronary artery bypass graft (CABG). In the EXCEL trial, those with DM treated for left main stem stenosis had similar outcomes (at 3 years) between PCI and CABG.
- ESC CAD intervention recommendations are outlined in Table 1.4.

Table 1.4 ESC recommendations for intervention in those with diabetes and coronary artery disease

Lesion	PCI	CABG
Single-vessel disease		
Without proximal LAD stenosis	Recommended	–
With proximal LAD stenosis	Equivalent	Equivalent
Two-vessel disease		
Without proximal LAD stenosis	Recommended	–

Table 1.4 (*Contd.*)

Lesion	PCI	CABG
With proximal LAD stenosis	–	Recommended
Three-vessel disease		
With low disease complexity (SYNTAX score 0–22)	–	Recommended
With intermediate or high disease complexity (SYNTAX score >22)	–	Recommended
Left main disease		
With low disease complexity (SYNTAX score 0-22)	Equivalent	Equivalent
With intermediate disease complexity (SYNTAX score 23–32)	–	Recommended
With high disease complexity (SYNTAX score ≥32)	–	Recommended

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LAD, left anterior descending (artery).

Reference

1. Vissere FLJ, *et al*. 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. 2023;**44**:4043–140.

Dyslipidaemias: overview

Lipoprotein metabolism

- *Cholesterol:* synthesized in the liver and combined with TGs into lipoproteins, which also contain apolipoprotein B (ApoB) used for synthesis of bile acids.
- *Very low-density lipoproteins (VLDLs):* ApoB-containing lipoproteins are secreted from the liver as VLDLs. These are hydrolysed, the TGs used for energy storage/consumption, and become TG-rich lipoprotein (TRL). TRL remnants are taken up by the liver or further hydrolysed to low-density lipoprotein (LDL).
- *LDLs:* mostly taken up by the liver to be metabolized and secreted into bile, some are taken up by other cells as a source of cholesterol.
- *High-density lipoproteins (HDLs):* HDL particles containing apolipoprotein A1 (ApoA1) transport excess cholesterol back to the liver. They do this directly or with cholesterol ester transfer protein (CETP) and exchange cholesterol for TGs with VLDL/LDL.
- *TGs:* transported either from the liver as VLDL for energy storage in adipose tissue or to muscle cells for energy consumption.
- *Ingested fat:* converted into TGs and combined with cholesterol and a short version of ApoB to produce chylomicrons (Fig. 1.6).[1]

Risk assessment

- Numerous epidemiological studies have confirmed that a direct relationship exists between LDL level and the risk of CAD.
- Therefore, it is essential to assess lipid levels in individuals who may be at ↑ risk.

Measure a fasting lipid profile if the patient

- Is a man aged >40 years or a woman aged >50 years
- Has CAD
- Has other risk factors for atherosclerosis
- Has clinical signs of hyperlipidaemia (xanthomata, xanthelasma, or corneal arcus)
- Has a family history of premature CAD or hyperlipidaemia

Practicalities of measurement

- Traditionally, lipid levels were measured while fasting. However, the difference between fasting and non-fasting levels is negligible and of no clinical significance. Therefore, it can be assumed that non-fasting samples have the same prognostic value as fasting samples.
- The following lipid analysis should be performed as standard:
  - Measurement of plasma TC levels, which is used to calculate CV risk by using the SCORE-2 system.
  - HDL levels can further refine risk stratification by using the SCORE-2 system.
  - LDL levels should be the primary analysis performed for screening and it is these levels that predominantly guide management.
  - TG assessment is also recommended, as this may identify those individuals who have a greater risk than is reflected in their LDL levels due to higher levels of atherogenic ApoB- and TG-containing lipoproteins.

- In the obese/those with DM/high TG levels/low LDL levels, measurement of LDL levels may underestimate the level of ApoB-containing lipoproteins. Therefore, ApoB levels should also be measured in these individuals.

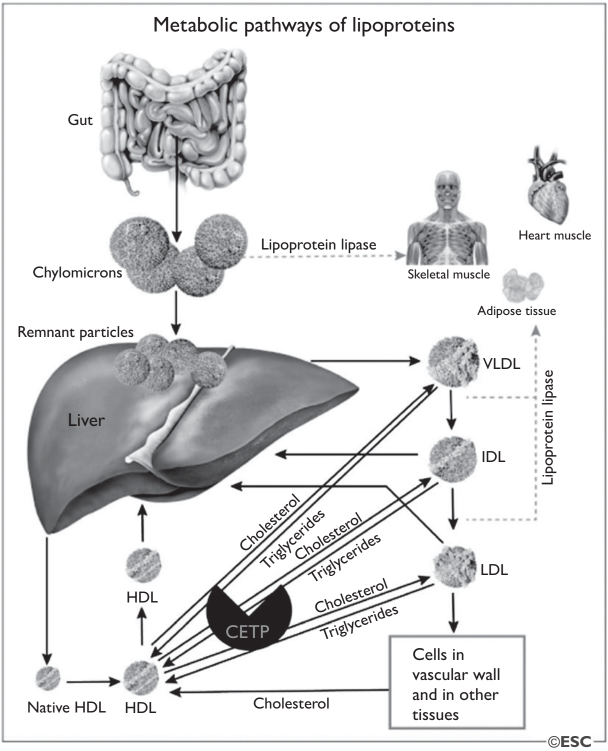
Metabolic pathways of lipoproteins
Gut
Chylomicrons
Lipoprotein lipase
Skeletal muscle
Heart muscle
Adipose tissue
Remnant particles
Liver
VLDL
IDL
LDL
Lipoprotein lipase
Cholesterol
Triglycerides
Cholesterol
Triglycerides
Cholesterol
Triglycerides
CETP
HDL
Native HDL
HDL
Cholesterol
Cells in vascular wall and in other tissues
©ESC

Fig. 1.6 Lipoprotein metabolism.

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Reference

1. Mach F, Baigent C, Catapano AL, *et al*. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J*. 2020;**41**:111–88. Available from: ✎ https://doi.org/10.1093/eurheartj/ehz826

Dyslipidaemias: management

Pharmacological agents

Statins

- Statins inhibit the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase enzyme in the liver, limiting cholesterol synthesis. The resulting ↓ cholesterol level stimulates LDL receptor expression, which leads to ↑ LDL uptake from blood.
- Statins also ↓ TG levels by around 10–20%, especially at high doses (atorvastatin, rosuvastatin) and ↑ HDL levels.
- Significant evidence has built up that strongly supports their use in primary and secondary prevention, and confirmed their safety.
- Large randomized clinical trials have shown a consistent reduction (25–30%) in the relative risk of major CV events with use of statins in primary (ASCOT, WOSCOPS, HPS, CARDS) and secondary prevention (MIRACL, CARE, LIPID, 4S, HPS). The Cholesterol Treatment Trialists (CTT) meta-analysis demonstrated a 20% ↓ in major vascular events per 1mmol/L ↓ in LDL levels.
- In the first outcome study comparing two statins, the PROVE-IT study showed that high-dose atorvastatin (80mg) was more effective than pravastatin (40mg) at reducing LDL levels, thereby preventing further major CV events during the first 2–3 years after presentation with ACS.

Cholesterol absorption inhibitors

- Ezetimibe inhibits the uptake of cholesterol (both dietary and biliary) from the intestine. This ↓ the amount of cholesterol delivered to the liver, which reacts by ↑ LDL receptor expression at the surface of hepatocytes and facilitates removal of LDL from blood.
- Ezetimibe ↓ LDL and TG levels and ↑ HDL levels. It has an additive effect on LDL reduction when combined with statins, bile acid sequestrants, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.
- The IMPROVE-IT trial was performed in patients following ACS. Patients were randomized to simvastatin 40mg or simvastatin plus ezetimibe. After 7 years, there were 170 fewer CV events in the dual therapy arm and the average LDL level was 1.4 vs 1.8mmol/L.

Bile acid sequestrants

- Bile acids are produced in the liver and then released into the intestine. Most bile acids are reabsorbed in the ileum.
- Colestyramine binds to bile acids and prevents reabsorption. The liver produces more bile acid from hepatic cholesterol, causing ↑ cholesterol demand. This leads to ↑ LDL receptor expression and ↓ LDL levels.

PCSK9 inhibitors

- PCSK9 leads to ↓ LDL receptors and therefore ↑ LDL levels.
- PCSK9 inhibitors are monoclonal antibodies that ↓ PCSK9 levels, which are unable to bind to LDL receptors. This leads to ↓ LDL levels.
- PCSK9 inhibitors are very effective at ↓ LDL levels (↓ of 60%, depending on the dose) alone, in combination with a statin, or where a statin is not tolerated in combination with ezetimibe. They also ↓ TG levels.

- The PCSK9 inhibitors currently licensed for use are alirocumab and evolocumab. They are administered by subcutaneous (s/c) injection.
- The FOURIER trial enrolled individuals with CAD and LDL levels >1.8mmol/L who were on a statin. Participants were randomized to evolocumab or placebo. In the evolocumab arm, LDL levels ↓ from 2.4 to 0.8mmol/L, with 15% ↓ in primary outcome (CV death, MI, hospitalization for angina, coronary revascularization, or CVA).
- The ODYSSEY trial enrolled individuals after hospitalization for MI/unstable angina (UA) who were on a statin with LDL levels >1.8mmol/L. Participants received alirocumab or placebo. LDL levels ↓ from 2.4 to 1.2mmol/L in the alirocumab arm, with 15% ↓ in the primary outcome (CAD death, non-fatal MI, UA hospitalization, or CVA).
- At present, these drugs are only cost-effective in high-risk patients.

Fibrates

- Gemfibrozil is a peroxisome proliferator-activated receptor (PPAR)-α (PPAR-α) agonist, which has a key role in lipid and lipoprotein metabolism.
- This leads to ↓ LDL and TG levels and ↑ HDL levels.
- The data are less robust with regard to CV outcomes, compared with statins.

n-3 fatty acids

- n-3 fatty acids ↓ TG levels; however, their mechanisms are poorly understood.
- Data on CV outcomes remain inconclusive, as many trials were conducted with lower doses. Trials using higher doses have demonstrated risk reduction; however, these results need to be corroborated.

Nicotinic acid

- This has shown no benefit and is not currently approved in Europe.

Novel therapies

Inclisiran

- Inclisiran is a small interfering RNA which targets PCSK9 messenger RNA and is administered s/c.
- The ORION-10 and ORION-11 studies randomly assigned individuals with atherosclerotic disease or atherosclerotic disease risk equivalent (type II DM, FH, 10-year risk of a CV event of ≥20%) to receive inclisiran or placebo, in addition to maximum-dose statin therapy. There was ~50% ↓ in LDL levels in those given inclisiran.

Icosapent ethyl

- Icosapent ethyl is a purified eicosapentaenoic acid ethyl ester, which lowers TG levels.
- The REDUCE-IT trial randomly assigned individuals with CVD/DM and risk factors, with high TG levels despite statin therapy, to icosapent ethyl or placebo. The risk of ischaemic events and CV death was significantly ↓ in the former group.

Bempedoic acid

- This reduces cholesterol synthesis by inhibiting adenosine triphosphate (ATP) citrate lyase. In the CLEAR Harmony trial, adding bempedoic acid to statins significantly ↓ LDL levels in patients with ACVD or FH.

Dyslipidaemias: guidelines and targets

Dyslipidaemia management

- After CV risk assessment, baseline LDL levels should be measured.
- A statin should be prescribed as first line and titrated to the highest dose tolerated (ESC Class I recommendation).
- Ezetimibe may be added if the target LDL level is not reached (ESC Class I recommendation).
- For primary prevention, addition of a PCSK9 inhibitor may be considered in patients at very high risk who do not meet their LDL target (ESC Class IIb recommendation).
- For secondary prevention, a PCSK9 inhibitor is recommended in very high-risk individuals if target LDL is not reached (ESC Class I recommendation).
- If statins are not tolerated, ezetimibe may be considered (ESC Class IIa recommendation) ± PCSK9 inhibitor (ESC Class IIb recommendation).

Hypertriglyceridaemia

- Statins are first line in high-risk individuals with TG >2.3mmol/L.

Monitoring

- Response to therapy should be monitored. There is no accepted time frame, but it is reasonable to reassess 6–8 weeks from initiation.

Treatment targets

- Normal ranges for plasma lipid levels are shown in Table 1.5. Lipid treatment targets are listed in Table 1.6.

Table 1.5 Normal ranges of plasma lipid levels

	Levels (mmol/L)	Levels (mg/dL)
Total cholesterol	4.0–6.5	150–250
LDL cholesterol	<4.1	<160
HDL cholesterol	0.8–2.0	30–75
Triglycerides	0.8–2.0	70–175

Table 1.6 Lipid treatment targets in low- to very high-risk individuals with coronary artery disease

Risk	LDL (mmol/L)	Non-HDL (mmol/L)	ApoB (mg/dL)
Very high*	<1.4	<2.2	<65
High	<1.8	<2.6	<80
Moderate	<2.6	<3.4	<100
Low	<3		

* In secondary prevention, all individuals are classified as very high risk.

Dyslipidaemias: familial conditions

- If familial dyslipidaemia is suspected, then the family should be seen in a lipid clinic.

Familial hypercholesterolaemia

- FH has a prevalence of 1:200–1:250.
- It is caused by loss-of-function mutations in the LDL receptor (95% of cases) and *ApoB* genes, or gain-of-function mutations in the *PCSK9* genes. This causes elevated levels of LDL.
- The risk of CAD is ↑ 10-fold and those affected develop CAD below the age of 55 (in men) and 60 years (in women).
- This is most commonly diagnosed by using the Simon Broome diagnostic criteria (see Box 1.3).
- FH should be suspected when TC levels >8mmol/L in an adult, if premature CVD in the patient or family member, or tendon xanthomata in the patient or family member with premature cardiac death in a family member.
- Cholesterol-lowering therapy should be instigated as soon as possible.

Homozygous familial hypercholesterolaemia

- Homozygous FH (HoFH) has a prevalence of 1:160,000–1:320,000.
- TC levels may reach >13mmol/L and patients present with marked xanthomata and CAD, often below the age of 20 years.
- Intensive cholesterol-lowering therapy should be instigated as soon as the condition is diagnosed.

Familial combined hyperlipidaemia

- Familial combined hyperlipidaemia (FCH) has a prevalence of 1:100–1:200.
- FCH is caused by a combination of genetic and environmental factors, and is characterized by elevated LDL and/or TG levels. This can lead to premature CAD.
- It is diagnosed on the basis of ApoB levels >120mg/dL and TG levels >1.5mmol/L, with a family history of premature CVD.

Familial dysbetalipoproteinaemia

- This is an autosomal recessive condition, which is caused by homozygosity of the E2 isoform of ApoE.
- This is essential for clearance of chylomicron remnants and intermediate-density lipoproteins. As a result, both TC and TG levels are elevated.
- Patients present with xanthomata over the knees and elbows, and in creases of the hands and wrists, and are at very high risk of CAD.
- This condition responds well to statin therapy.

Hypertriglyceridaemia

- Hypertriglyceridaemia is an autosomal recessive condition caused by mutations in several genes (*LPL*, *ApoC2*, *ApoA5*, *LMF1*, *GPIHBP1*, and *GPD1*) involved in VLDL production and removal.
- Hypertriglyceridaemia can lead to chylomicronaemia, with TG levels of >11.2mmol/L, lipid deposits, and pancreatitis.

Box 1.3 Simon Broom diagnostic criteria

DEFINITE

High cholesterol levels	Children (<16 years)	TC >6.7mmol/L, LDL-C >4mmol/L
	Adults	TC >7.5mmol/L, LDL-C >4.9mmol/L
And at least one of:		
Physical findings	Tendon xanthomas or evidence of these signs in first- or second-degree relatives	
Genetic evidence	DNA-based evidence of LDL receptor, *PCSK9*, or *ApoB-100* mutation	

POSSIBLE

Cholesterol levels as above and at least one of the following:

1. Family history of MI at age <50 years in second-degree relative or <60 years in first-degree relative
2. Family history of raised TC level >7.5mmol/L in adult first- or second-degree relative or >6.7mmol/L in child, brother, or sister aged <16 years.

Source: data from Risk of fatal coronary heart disease in familial hypercholesterolemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ* 1991;**303**:893–6; Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. *Atherosclerosis* 1999;**142**:105–12.

Hypertension: overview

Epidemiology

- The prevalence of hypertension is around 30–45%.
- The prevalence ↑ with age and is 60% in those aged over 60 years.
- An estimated 1.5 billion individuals will have hypertension by 2025.

Definition

- Hypertension is defined as SBP of >140mmHg and/or DBP of >90mmHg.
- The classification of BP is shown in Table 1.7.

Table 1.7 Classification of blood pressure

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	<130	<85
High normal	130–139	85–89
Grade 1 hypertension	140–159	90–99
Grade 2 hypertension	160–179	100–109
Grade 3 hypertension	≥180	≥110
Isolated systolic hypertension	≥140	<90

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Aetiology

- Most individuals (>95%) have essential (primary) hypertension, in which an underlying cause for the hypertension is not found.
- There are many causes of secondary hypertension (see Box 1.4).

Box 1.4 Causes of secondary hypertension

Renal disease

- Renal artery stenosis, polycystic kidneys

Endocrine disease

- Conn's and Cushing's syndromes, phaeochromocytoma, acromegaly, hyperparathyroidism

Other

- Aortic coarctation, pregnancy-induced hypertension and pre-eclampsia, obesity, excessive dietary salt or liquorice intake

Drugs

- Examples: oral contraceptive pill, steroids, cancer therapy (e.g. vascular endothelial growth factor, tyrosine kinase inhibitors)
- Illicit stimulants (e.g. amphetamine, MDMA, cocaine)

Basic pathology

- Chronic and/or severe hypertension may lead to a spectrum of structural and functional changes in organs and the vasculature. This may specifically affect the brain, eyes, heart, kidneys, and vessels.

End-organ damage

- *Cardiac:* ↑ left ventricular (LV) mass, MI, HF.
- *Renal:* microalbuminuria, proteinuria, CKD.
- *Cerebrovascular:* transient ischaemic attack (TIA), CVA.
- *Vascular:* arterial stiffening, peripheral arterial disease (PAD).
- *Ophthalmic:* retinopathy.

Diagnosis

- All adults should be made aware of their BP.
- If <120/80mmHg, BP should be measured every 5 years.
- In those with a normal BP, this should be repeated every 3 years, and annually in those with high-normal BP.
- BP may be measured in clinic on repeated visits (except when hypertension is severe) or by using out-of-office readings.

Clinic readings

- Patients should be seated for 5min.
- BP should be measured in both arms by using an appropriate cuff size.
- Three readings should be taken, 1–2min apart.
- Where there is a higher BP in one arm, compared with the other, the higher value should be recorded.

'Out-of-office' readings

- Home BP monitoring is an average reading of BP readings measured ideally for 6–7 consecutive days before a clinic visit, with readings taken twice a day (morning and evening).
- Ambulatory monitoring provides an average BP taken usually over 24h. The machine takes readings at 15–30min intervals.
- The definition of hypertension varies, depending on the type of reading taken (see Table 1.8).

Table 1.8 Definition of hypertension according to mode of measurement

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Clinic BP	≥140	≥90
Ambulatory BP		
Daytime mean	≥135	≥85
Night-time mean	≥120	≥70
24h mean	≥130	≥80
Home BP mean	≥135	≥85

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Hypertension: clinical features

History

- It is important to explore whether an individual has any evidence of end organ damage.
- *Cardiac:* chest pain, shortness of breath, peripheral oedema, palpitations, syncope, history of MI/HF.
- *Renal:* thirst, polyuria, haematuria, nocturia, history of CKD.
- *Cerebrovascular:* weakness, sensory disturbance, headache, diplopia, unsteadiness, history of TIA/CVA.
- *Vascular:* cold extremities, intermittent claudication, rest pain, history of peripheral revascularization.
- *Ophthalmic:* visual disturbance.

Examination

- Full CV examination (including listening for carotid bruits, and assessing for radiofemoral delay (coarctation) and peripheral arterial pulses).
- Abdominal examination (polycystic kidneys, renal bruits (renal artery stenosis)).
- Neurological examination and fundoscopy (see Box 1.5) are recommended in all patients with grade 2/3 hypertension and all those with DM.

Box 1.5 Grading of hypertensive retinopathy

- Grade 1: tortuous arteries, with thickened bright walls ('silver wiring')
- Grade 2: arteriovenous nipping (narrowing in vein crossed by an artery)
- Grade 3: flame haemorrhages and cotton wool spots (small retinal bleeds and exudates)
- Grade 4: papilloedema

General clues to secondary causes of hypertension

- Early-onset hypertension (patients aged <40 years).
- Known renal disease.
- Recreational drug use.
- Pregnancy and oral contraceptive use.

Common causes of secondary hypertension

Vascular

Coarctation of the aorta

(See ➲ Acyanotic defects: coarctation of the aorta, pp. 356–7.)

Renal

Intrinsic renal disease

- Glomerulonephritis, systemic sclerosis, chronic pyelonephritis, polycystic kidney disease.

Renovascular disease

- Atheroma, fibromuscular dysplasia.

Endocrine

Cushing's syndrome

- A disorder resulting from an excess of corticosteroid.
- *History:* weight gain, mood change, proximal muscle weakness/irregular menstruation, hirsutism, erectile dysfunction.
- *Examination:* moon facies, buffalo hump, supraclavicular fat pad, bruises, striae, central obesity, osteoporosis.

Phaeochromocytoma

- Tumour of chromaffin cells in the adrenal gland, which produces catecholamines.
- *History:* sweating, headaches, palpitations.
- *Examination:* tachycardia, pyrexia, abdominal pain over tumour, abdominal mass.

Acromegaly

- A condition caused by excess growth hormone (GH), usually secondary to a tumour in the pituitary gland.
- *History:* change in hand or feet size, headache, visual loss, acroparaesthesia.
- *Examination:* prominent supraorbital ridge, coarse facies, macroglossia, widely spaced teeth, carpal tunnel, proximal weakness.

Hyperparathyroidism

- A disorder characterized by ↑ circulating parathyroid hormone (PTH), can be due to a variety of causes, including pituitary adenoma and CKD.
- *History:* fatigue, mood changes, thirst, abdominal pain, bony pain, fractures.
- *Examination:* abdominal pain, bony pain.

Hyperaldosteronism

- A condition characterized by ↑ circulating aldosterone produced by the adrenal gland. Can be due to adrenal hyperplasia or adenoma.
- *History:* muscle weakness, cramps, headaches.
- *Examination:* weakness, paraesthesiae.

Hypertension: investigations

General investigations

- *Bloods:* full blood count (FBC), urea and electrolytes (U&Es) (renal disease), glucose/HbA1c, lipid profile.
- *Urinalysis:* urinary protein, ideally albumin:creatinine ratio to detect elevation in albumin excretion, pregnancy test if indicated.
- *Electrocardiogram (ECG):* may demonstrate LV hypertrophy (LVH).
- Other tests to assess end organ dysfunction further may be considered and include:
  - *Echocardiography:* to assess cardiac structure and function.
  - *Carotid ultrasound (US):* to determine plaque burden.
  - *Ankle–brachial pressure index (ABPI):* to screen for PAD.
  - *Magnetic resonance imaging (MRI)/computed tomography (CT) head:* to assess for ischaemia or haemorrhage.

Investigations for specific causes

If secondary hypertension is suspected, further investigation should focus on the possible underlying cause:

- *Polycystic kidneys:* abdominal US.
- *Renal artery stenosis/coarctation of the aorta:* magnetic resonance angiography (MRA) of the aorta and renal arteries.
- *Phaeochromocytoma:* 24h urine for metanephrines/metadrenaline.
- *Cushing's syndrome:* 24h urinary free cortisol.
- *Conn's syndrome:* plasma renin–aldosterone levels.
- *Acromegaly:* GH levels and if high, OGTT.
- *Hyperparathyroidism:* calcium and PTH levels.

Hypertension: management

- A 10/5mmHg ↓ in SBP and DBP, respectively ↓ major CV events by 20% and all-cause mortality by 5–10%. As such, aggressive management of hypertension is advised.
- When to start treatment depends on hypertension severity (see Fig. 1.7).

Treatment targets

- Those with suspected secondary hypertension, young patients (<40 years), and those with hypertension resistant to treatment should be managed in a hospital outpatient setting. Those with sudden onset of malignant hypertension should be managed as an inpatient (see ➔ Malignant hypertension, pp. 40–1).
- The SPRINT trial compared a target of SBP <140mmHg to SBP <120mmHg in >9000 patients with high CV risk. A more aggressive approach to BP lowering led to a 25% ↓ in CV events and 27% ↓ in all-cause mortality.
- ESC guidelines recommend lowering the BP to 140/90mmHg and, if tolerated, aiming to reduce the BP to 130/80mmHg.

Older individuals

- In older individuals with a greater number of comorbidities, reducing SBP to <120mmHg appears to ↑ the risk of harm.
- *In patients >65 years*, aim SBP 130–140mmHg and DBP <80mmHg.
- *In older individuals (65–80 years)*, initiate BP-lowering management if BP >140–159mmHg.
- *In elderly individuals (>80 years)*, initiate BP-lowering management if BP ≥160mmHg.

Non-pharmacological intervention

- *Dietary sodium reduction:* advised target of <5g per day. Each 1g/day less sodium is associated with 1mmHg ↓ SBP.
- *Moderated alcohol intake:* National Institute for Health and Care Excellence (NICE) guidance suggests <14 units/week.
- *Dietary changes:* ↑ dietary intake of fresh fruits, vegetables, nuts, unsaturated fatty acids, and low-fat dairy products; ↓ in red meat.
- *Weight loss:* aiming for BMI of 20–25kg/m^2 and normal waist circumference (<94cm in men and <80cm in women).
- ↑ *in physical activity:* aiming for 150min of moderate, or 75min of vigorous, activity per week in addition to resistance exercise twice a week.

Pharmacological intervention

- Although NICE guidelines suggest monotherapy with an ACEi or a CCB for hypertension, ESC guidelines reflect the fact that most patients will require combination therapy in order to achieve a BP of 130/80mmHg more rapidly.
- Low-dose combination therapy may be more efficacious than maximum-dose monotherapy, and is generally safe and well tolerated.
- Fig. 1.8 illustrates when and how to initiate BP-lowering therapies.

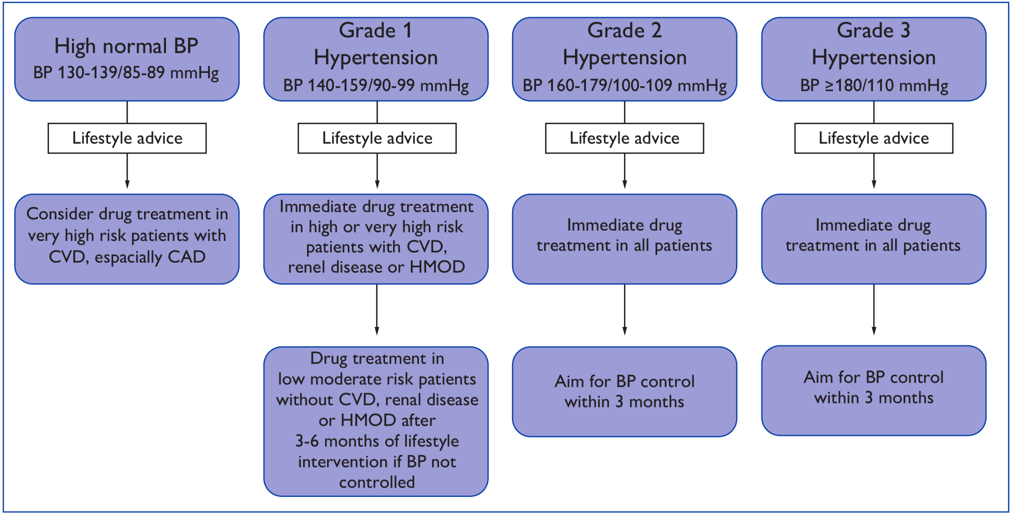
High normal BP
BP 130-139/85-89 mmHg
Lifestyle advice
Consider drug treatment in very high risk patients with CVD, espacially CAD
Grade 1 Hypertension
BP 140-159/90-99 mmHg
Lifestyle advice
Immediate drug treatment in high or very high risk patients with CVD, renel disease or HMOD
Drug treatment in low moderate risk patients without CVD, renal disease or HMOD after 3-6 months of lifestyle intervention if BP not controlled
Grade 2 Hypertension
BP 160-179/100-109 mmHg
Lifestyle advice
Immediate drug treatment in all patients
Aim for BP control within 3 months
Grade 3 Hypertension
BP ≥180/110 mmHg
Lifestyle advice
Immediate drug treatment in all patients
Aim for BP control within 3 months

Fig. 1.7 Initiation of blood pressure-lowering interventions. HMOD, hypertension-mediated organ damage.

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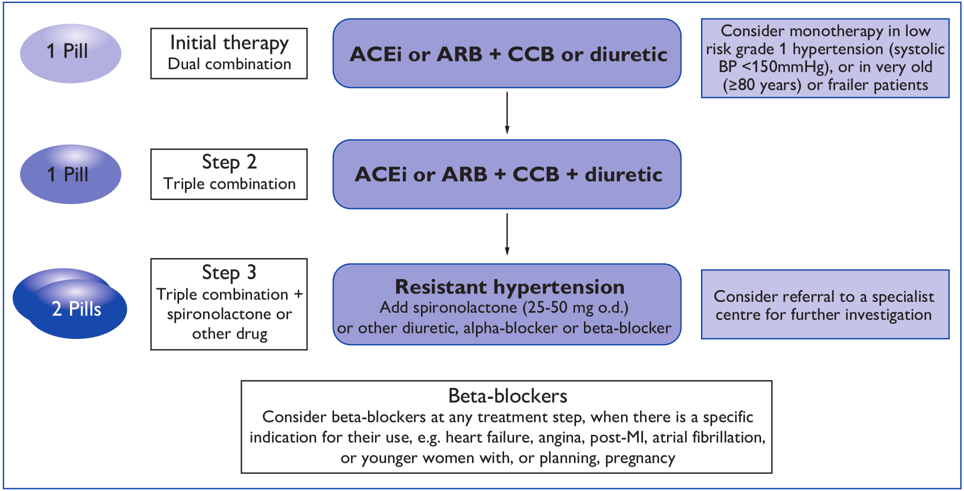
1 Pill
Initial therapy
Dual combination
ACEi or ARB + CCB or diuretic
Consider monotherapy in low risk grade 1 hypertension (systolic BP <150mmHg), or in very old (≥80 years) or frailer patients
1 Pill
Step 2
Triple combination
ACEi or ARB + CCB + diuretic
2 Pills
Step 3
Triple combination + spironolactone or other drug
Resistant hypertension
Add spironolactone (25-50 mg o.d.)
or other diuretic, alpha-blocker or beta-blocker
Consider referral to a specialist centre for further investigation
Beta-blockers
Consider beta-blockers at any treatment step, when there is a specific indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation, or younger women with, or planning, pregnancy

Fig. 1.8 Pharmacological management of hypertension. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

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Follow-up

- Following initiation of antihypertensive medications, review should be performed at 2 months.
- Once the target BP is achieved, an individual may be seen every 6 months. Risk factors and organ damage should be assessed at least every 2 years.

Malignant hypertension

Definition

- Malignant hypertension is a medical emergency requiring immediate treatment to prevent acute end organ damage.
- Diagnosed on the basis of ≥ grade 3 hypertension associated with new or worsening target organ dysfunction.

Clinical features

- Patients may present with a headache (oedema secondary to failure of cerebral circulation autoregulation) or visual disturbances (oedema/retinopathy). If a patient has hypertensive encephalopathy, they may present with tonic–clonic seizures and loss of consciousness.
- Patients may also experience chest pain (myocardial ischaemia) and shortness of breath (congestive cardiac failure (CCF)).

Investigations

- *Bloods* (see Box 1.6).
- *Urine:* haematuria/proteinuria; consider toxicology if suspicion of ingestion of illicit substances.
- *ECG:* assessment of ongoing ischaemia/infarction, possible LVH if hypertension is long-standing.
- *Chest X-ray (CXR):* assessment of pulmonary oedema.
- *Fundoscopy:* assessment of hypertensive changes (see Box 1.5).
- *CT/MRI:* if neurological symptoms present.
- *Renal US:* for assessment of renal arteries once the patient is stable (MRA of the renal arteries is the gold standard where available).

Box 1.6 Bloods tests in malignant hypertension

- FBC and blood film (microangiopathic haemolytic anaemia may occur—if suspected, lactate dehydrogenase, haptoglobin, and indirect bilirubin levels should also be requested)
- U&Es (detection of renal dysfunction)
- Troponin, NT-proBNP (detection of acute coronary syndromes/heart failure)

Prognosis

- If left untreated, 1-year mortality is around 90%.

Management

- Aim of management is to reduce mean arterial pressure by 20–25%.
- *Labetalol:* should be administered in 20mg boluses IV every 10min or given as a 0.5–2mg/min IV infusion until the intended reduction in BP is achieved. The maximum dose should not exceed 300mg. Generally considered an appropriate first-line agent in those presenting with a hypertensive emergency, except if in acute cardiogenic pulmonary oedema.
- *Nicardipine:* given as 5–15mg/h IV infusion. Recommended in those presenting with a hypertensive emergency with or without renal failure or in those with hypertensive encephalopathy.

- *Sodium nitroprusside:* second-line agent; administer as an infusion of 0.3–0.5mcg/kg/min, ↑ by 0.5mcg/kg/min every 5min until goal BP is achieved. The maximum dose should not exceed 10mcg/kg/min.
- *Glyceryl trinitrate (GTN):* given as 0.5–10mg/h IV infusion. Recommended as a first-line agent in those presenting with a hypertensive emergency associated with an acute coronary event, acute cardiogenic pulmonary oedema, or acute aortic dissection.

Chronic coronary syndromes: overview

Definition

- The 2019 ESC guidelines on chronic coronary syndromes (CCS)[1] separate these into:
    1. Stable angina and/or dyspnoea and suspected CAD
    2. New-onset HF and suspected CAD
    3. Asymptomatic and symptomatic individuals with stabilized symptoms <1 year after ACS or recently revascularized
    4. Asymptomatic and symptomatic individuals >1 year post-diagnosis or revascularization
    5. Angina with vasospasm/microvascular angina
    6. Asymptomatic individuals with CAD on screening.
- These scenarios all confer different risks of CV events.

Clinical features

History

- *Typical angina:* meets all the criteria outlined in Box 1.7.
- *Atypical angina:* meets two out of three criteria.
- *Non-anginal chest pain:* meets none of the criteria.
- Anginal pain lasts for <10min and usually a few minutes or less.
- Angina may also be associated with dyspnoea, nausea, and clamminess. It is important to note that angina may be paradoxically reduced on further exercise (walk-through angina) or on second exertion (warm-up angina).

Box 1.7 Features of typical cardiac chest pain

- Chest pain which may also radiate to the neck, jaw, shoulder, or arm
- May be brought on by physical exertion
- Relieved by nitrates within 5min

Stable vs unstable angina

- *Stable angina:* characterized by pain occurring after a relatively constant level of exertion
- *UA:* characterized by pain on minor exertion or at rest. Is either of new onset or a dramatic worsening of existing symptoms
- *Crescendo angina:* characterized by pain on reducing levels of exertion, usually over a period of days
- *Decubitus angina:* provoked by lying flat

Differential diagnosis of angina

- Aortic dissection
- Pericarditis
- Pneumothorax, pneumonia, pulmonary embolus
- Oesophageal pathology (inflammation/spasm)
- Upper gastrointestinal pathology (gastritis, peptic ulcer, pancreatitis, cholecystitis)
- Musculoskeletal chest wall pain

- The *Canadian Cardiovascular Society (CCS)* (see Box 1.8) system provides a quantitative means to describe exertional capacity and is divided into four classes.

Box 1.8 CCS classification of angina

I. Minimal limitation of ordinary activity. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation
II. Slight limitation of ordinary activity; angina occurs on walking or climbing stairs rapidly; walking in cold, in wind, or under emotional stress
III. Marked limitation of ordinary physical activity; angina occurs on walking 50–100m on level ground or climbing one flight of stairs at a normal pace in normal conditions
IV. Inability to perform any physical activity without discomfort; angina symptoms may be present at rest

Examination

- *Peripheral pulse rate:* this may be slowed by inferior ischaemia affecting the atrioventricular (AV) node. A resting tachycardia, if present, usually represents activation of the sympathetic nervous system but may be due to an arrhythmia precipitated by ischaemia.
- *BP*: to look for hypertension (predisposing to atheroma) or hypotension (due to cardiac dysfunction or over-medication).
- *Precordial examination:* palpation of the apex beat for LVH and cardiac enlargement, auscultation for added heart sounds (HF or acute ischaemia), aortic stenosis (AS) or mitral regurgitation (MR) (due to papillary muscle dysfunction).
- *Features of HF:* listen for crepitations at the lung bases, dependent pitting oedema (typically bilateral ankle ± leg oedema; sacral oedema may also occur).
- *Features of peripheral vascular disease:* palpate for aortic aneurysm; feel the carotid and limb pulses; listen for carotid, renal, or femoral artery bruits; assess tissue integrity and capillary refill of the legs and feet.
- *Features of hypercholesterolaemia:* xanthelasma around the eyes, corneal arcus, and xanthoma of the skin and tendons.

Reference

1. Knuuti J, Wijns W, Sarasta A, *et al*. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;**41**:407–77.

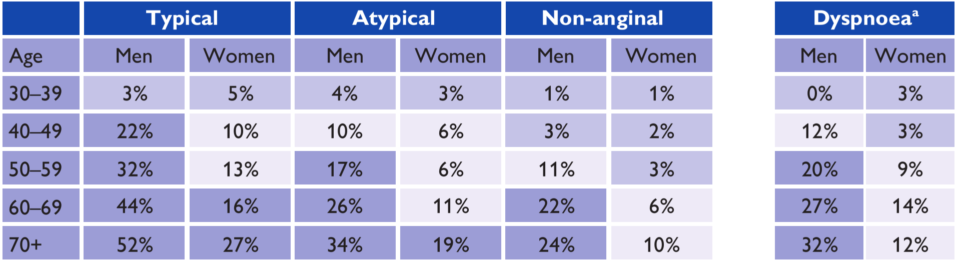
CCS: investigations

Basic testing

- *Bloods:* FBC, U&Es, lipid profile, HbA1c.
- *ECG:* may demonstrate ST-segment depression, pathological Q waves, conduction abnormalities, and arrhythmias. Dynamic ST-segment changes are diagnostic of vasospasm when accompanied by angina.
- *CXR:* should be performed if there is suspicion of HF, pulmonary pathology, or an abnormality of the bony structures of the chest wall.
- *Echocardiography:* provides essential information regarding LV function. ↓ LV function ± regional wall motion abnormalities (RWMAs) in a coronary territory suggest previous MI. Echocardiography may also provide information regarding other pathologies such as valvular heart disease, cardiomyopathies, and HF.
- *Exercise ECG:* exercise ECG is not a useful tool to rule in or out CAD. It is of no diagnostic value in individuals with ECG changes that affect interpretation such as resting ST changes (left bundle branch block (LBBB), paced, ST-segment depression, or those taking digoxin). However, it may be useful for assessment of symptoms, exercise tolerance, and BP response. ST-segment depression at a low workload with concomitant angina, as well as ectopy, arrhythmias, or abnormal BP response, are indicators of high risk of cardiac mortality.
- *MRI:* consider if echocardiography is inconclusive.

Assessment of pre-test probability of coronary artery disease

- Pre-test probability (PTP) refers to the likelihood that a patient has obstructive CAD (see Fig. 1.9).
- Diagnostic testing is likely to be useful when this PTP is intermediate (5–15%).
- Patients with a PTP of <5% have such a low probability of disease that diagnostic testing for CAD is not recommended.
- Significant risk factors, ECG abnormalities, LV dysfunction, or abnormal exercise testing may modify the PTP in favour of diagnostic testing.



	Typical		Atypical		Non-anginal		Dyspnoea[a]	
Age	Men	Women	Men	Women	Men	Women	Men	Women
30–39	3%	5%	4%	3%	1%	1%	0%	3%
40–49	22%	10%	10%	6%	3%	2%	12%	3%
50–59	32%	13%	17%	6%	11%	3%	20%	9%
60–69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

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Fig. 1.9 Pre-test probability tables in men and women.

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CCS: selection of testing modality

- In patients in whom revascularization is unlikely to be an option (e.g. multiple comorbidities), medical therapy should be instituted without the need for further investigation.
- Individuals with intermediate PTP in whom CAD cannot be excluded by clinical evaluation alone should undergo either non-invasive anatomical or functional imaging.

Functional non-invasive tests

- This includes stress echocardiography, stress cardiac magnetic resonance (CMR), and perfusion single-photon emission CT (SPECT) (see ➔ Dobutamine stress echocardiography, pp. 516–17; CMR:coronary artery disease, pp. 552–3; Myocardial perfusion scintigraphy, pp. 562–3).
- This is the preferred modality if there is a high likelihood of CAD; revascularization is an option and viability assessment is also required.
- Ischaemia may be provoked pharmacologically or on exercise.
- These tests have a high correlation with invasive fractional flow reserve (FFR) but are unable to provide information on non-obstructive coronary disease. Therefore, in the absence of ischaemia, patients should still receive risk factor modification.

Anatomical non-invasive tests

- This includes CT coronary angiography (CTCA) (see ➔ Cardiac CT: coronary angiography, pp. 538–9).
- This is the preferred modality if there is a low clinical likelihood of CAD, there is no previous history of CAD, and information on atherosclerosis is required.
- If a patient is obese, or has an irregular heartbeat or extensive coronary calcification, CTCA is not recommended due to poor diagnostic images.
- Stenoses of between 50% and 90% on CTCA may not be functionally significant. Therefore, invasive coronary angiography or functional non-invasive testing may be required.
- CTCA has shown great promise in the management of those with CAD. In the SCOT-HEART trial, patients with angina were randomized to standard care alone or standard care and CTCA. CTCA enabled clarification of the diagnosis, ↑ preventative and antianginal therapies, and ↓ the need for non-functional imaging. At 5 years, the rates of death from CAD or non-fatal MI were ↓ in the CTCA group, compared with standard care, with no significanl ↑ in invasive angiography or revascularization.
- Moreover, CT-guided FFR has been shown to be comparable with invasive FFR measurements. The FORECAST trial has also shown that compared with routine management, use of CT-guided FFR reduced the need for invasive angiography.

Invasive coronary angiography

- Individuals with a high PTP of CAD, with symptoms unresponsive to antianginal medication and low-effort angina, and risk stratified as high risk, should proceed directly to invasive angiography.
- FFR is the ratio of the pressure distal (Pd) to a stenosis, compared with the pressure proximal to a stenosis (Pa), during hyperaemia induced by

a vasodilator (usually adenosine). An FFR of ≤0.8 suggests significant stenosis.

- FFR is considered the gold standard for invasive assessment of coronary stenosis and should be performed in those with lesions between 50% and 90%, as FFR has been shown to change management strategies in up to 50% of individuals.
- Instantaneous wave-free ratio (iFR) is a non-hyperaemic pressure-based measure of coronary stenosis. During diastole, the wave-free period describes the time the waves that normally affect coronary flow are quiescent and Pd and Pa are linearly related. An iFR of ≤0.89 suggests significant stenosis.
- Although FFR is well accepted and validated, iFR offers an attractive alternative as it can reduce procedure time and the patient does not suffer the side effects of vasodilating agents.

Definition of high-risk individuals

(See Table 1.9)

Table 1.9 High-risk individuals defined according to different testing modalities

Modality	Criteria
Exercise ECG	Duke treadmill score >3%/year
SPECT/PET perfusion	Ischaemia ≥10% of the LV myocardium
Stress echocardiography	≥3 of 16 segments hypokinetic/akinetic
CMR	≥2 of 16 segments with stress perfusion defects/ ≥3 dobutamine-induced dysfunctional segments
CTCA/invasive coronary angiography	Triple-vessel disease with proximal stenoses, left main disease, or proximal left anterior descending artery
Invasive FFR/iFR	≤0.8/≤0.89

SPECT, single-photon emission computed tomography; PET, positron emission tomography; LV, left ventricular; CMR, cardiac magnetic resonance; CTCA, computed tomography coronary angiography; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio.

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CCS: medical management

Risk factor management

- *CAD:* risk factor modification (see ➔ CAD: risk factor modification, pp. 14–15).
- *Hypertension:* investigation and management (see ➔ Hypertension: investigation, p. 34; Hypertension: management, pp. 36–9).
- *DM:* management in CVD (see ➔ DM: management in athersclerotic CVD, pp. 18–21).
- *Dyslipidaemias:* guidelines and targets (see ➔ Dyslipidaemias: guidelines and targets, p. 26).

Cardiovascular event prevention

Aspirin

- Low-dose aspirin (75mg once daily (od)) (or clopidogrel 75mg od if intolerant) is recommended for the prevention of ischaemic events in those with previous MI/revascularization. The Antithrombotic Trialist's Collaboration concluded that post-MI, aspirin reduced the risk of further CV events by 25%.
- In those with CAD without a previous MI, aspirin can be considered.

Aspirin and rivaroxaban

- The COMPASS trial compared low-dose rivaroxaban (2.5mg twice daily (bd)) and aspirin (100mg od), rivaroxaban (5mg bd) with placebo, or aspirin (100mg od) with placebo in those with CCS or peripheral vascular disease. The composite outcome of MI, CV death, or CVA was 24% ↓ in the rivaroxaban and aspirin arm than with aspirin alone. However, there was a higher bleeding rate (3.1% vs 1.9%). Higher-dose rivaroxaban conveyed a significantly ↑ risk of bleeding, but no benefit on the primary outcome.
- Combination of low-dose rivaroxaban and aspirin can be considered in those at high risk of ischaemic events.

Antianginal therapy

- Reducing angina symptoms should be a central aim of therapy, with response to antianginal therapy assessed at 2–4 weeks. (For further information on listed medications, see ➔ Chapter 17.)

β-blockers and calcium channel blockers

- Either a β-blocker or a dihydropyridine (DHP) CCB (e.g. amlodipine, nifedipine) is recommended as first-line therapy.

Contraindications

- β-blockers are contraindicated in those with higher-degree heart block (second degree and above) and critical limb ischaemia. Asthma is a relative contraindication.
- β-blockers should be monitored closely if combined with a non-DHP CCB (if heart rate (HR) >80bpm) due to the risk of worsening HF, AV block, and severe bradycardia. The combination of verapamil and a β-blocker should generally be avoided.

- Non-DHP CCB should be avoided in HF due to the risk of further depressing cardiac function.

Nitrates

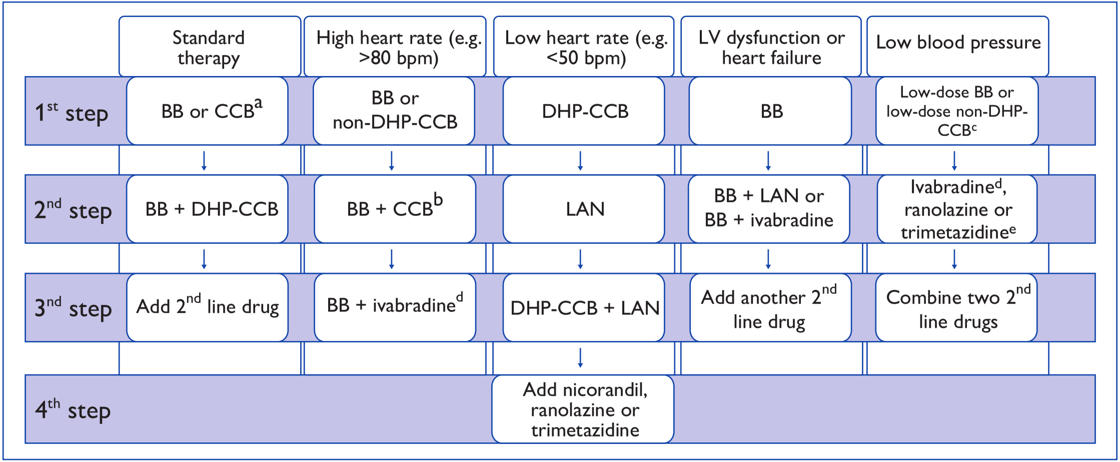
- S/L glyceryl trinitrate formulations provide effective short-term relief of anginal symptoms. The patient should be educated about the appropriate manner in which to administer therapy safely and effectively. The patient should sit down and take doses at 5min intervals. If angina persists beyond 15min, they should call an ambulance.
- Long-acting nitrate (LAN) formulations, such as isosorbide mononitrate (ISMN) and isosorbide dinitrate (ISDN), are second-line therapy for angina relief when a β-blocker and a CCB are insufficient or contraindicated.
- If taken regularly, nitrate tolerance may develop. Dosing should be arranged to allow for an overnight nitrate-free period.

Contraindications

- Nitrates are contraindicated in those with severe AS or hypertrophic cardiomyopathy (HCM), and should not be administered with phosphodiesterase inhibitors due to the risks of severe hypotension.

Second-line agents

- *Ivabradine:* inhibits the funny current (I_f) and slows HR. Should only be used when HR is >70bpm and the patient is in sinus rhythm (SR).
- *Ranolazine:* inhibits the late inward sodium channel. It can prolong the QT interval, which should be monitored during therapy.
- Ivabradine and ranolazine do not have significant effects on BP.
- *Nicorandil:* a nitrate derivative of nicotinamide. This is contraindicated in severe hypotension.
- *Trimetazidine:* improves glucose utilization through inhibition of fatty acid oxidation. Contraindicated in Parkinson's disease and movement disorders.
- Antianginal agents may be used in different combinations, depending on the clinical picture. Fig. 1.10 shows how medications may be administered together, depending on BP, HR, and LV dysfunction.



	Standard therapy	High heart rate (e.g. >80 bpm)	Low heart rate (e.g. <50 bpm)	LV dysfunction or heart failure	Low blood pressure
1st step	BB or CCB[a]	BB or non-DHP-CCB	DHP-CCB	BB	Low-dose BB or low-dose non-DHP-CCB[c]
	↓	↓	↓	↓	↓
2nd step	BB + DHP-CCB	BB + CCB[b]	LAN	BB + LAN or BB + ivabradine	Ivabradine[d], ranolazine or trimetazidine[e]
	↓	↓	↓	↓	↓
3rd step	Add 2nd line drug	BB + ivabradine[d]	DHP-CCB + LAN	Add another 2nd line drug	Combine two 2nd line drugs
			↓		
4th step			Add nicorandil, ranolazine or trimetazidine		

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Fig. 1.10 Antianginal therapies based on clinical parameters. BB, β-blocker; CCB, calcium channel blocker; DHP, dihyropyridine; LAN, long-acting nitrate.

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CCS: revascularization

- Revascularization should be considered as an adjunct to, not a replacement for, medical therapy.
- In recent years, a number of trials have attempted to address whether or not revascularization conveys benefit over and above medical therapy in individuals with stable CAD.
- *ORBITA:* a double-blinded trial in which symptomatic individuals with severe single-vessel stenosis were randomized to either optimal medical therapy (OMT) and PCI or OMT and a sham procedure. PCI did not ↑ exercise capacity by more than the effect of a placebo.
- *ISCHAEMIA:* sought to identify whether revascularization provided additional clinical benefit in those individuals with stable CAD and ≥ moderate ischaemia on stress testing. Patients were randomized to OMT and revascularization or to OMT and revascularization only in the event of failure of OMT. An initial invasive strategy did not convey any additional benefit over a median of 3 years in the primary composite end point of MI, CV death, hospitalization for UA, HF, and resuscitated cardiac arrest. However, the rates of spontaneous MIs ↓ in the revascularization group and revascularization was more likely to ↓ angina symptoms.
- *FAME-2:* assessed OMT vs OMT and PCI in those with FFR <0.8. At 5-year follow-up, there were ↓ rates of the primary end point of death, MI, and urgent revascularization in the intervention arm. In addition, relief from symptoms was ↑ in the PCI group.
- These conflicting results suggest that decisions should be made on the basis of an individual's risk, benefit, and personal preferences.
- The current guidelines, published prior to the findings of longer-term follow-up in the ISCHAEMIA trial, are discussed below.

Management of symptomatic patients

- Patients with angina and documented ischaemia (>10% of LV) in the absence of multivessel disease should be considered for revascularization, in addition to medical therapy.
- In the presence of symptoms and multivessel disease, lesions with FFR <0.8 may be considered for revascularization, in addition to medical therapy.
- If there is no evidence of ischaemia, revascularization may be considered in the presence of >90% stenosis, FFR <0.8, and left ventricular ejection fraction (LVEF) <35% (secondary to CAD), in addition to medical therapy.

Management of asymptomatic patients

- If patients have large areas of ischaemia (>10%), revascularization may be considered, in addition to medical therapy.
- If there is no evidence of ischaemia, revascularization may be considered in the presence of >90% stenosis, FFR <0.8, and LVEF <35% (secondary to CAD), in addition to medical therapy.

CCS: management of antiplatelets and anticoagulation

Periprocedural management

- Generally, interruption of warfarin should be avoided. However, a direct oral anticoagulant (DOAC) should be stopped for 12–48h before elective PCI.
- Unfractionated heparin (UFH) should be used as anticoagulation during the procedure.

Post-procedural management

- Aspirin 75mg od, in combination with clopidogrel 75mg, is recommended post-stenting for at least 6 months (ESC Class I recommendation). Prasugrel or ticagrelor should be considered in complex PCI procedures such as left main stenting or chronic total occlusion procedures.
- In those with low bleeding risk (low HASBLED score; see Table 1.10) and high risk of thrombotic events, DAPT may be extended >6 months and ≤30 months (ESC Class IIb recommendation).
- In patients with a high bleeding risk, 3 months of DAPT should be considered (ESC Class IIa recommendation).
- Following DAPT, lifelong single antiplatelet therapy (usually aspirin) is recommended.

Table 1.10 HASBLED score

Risk factor	Score	
Hypertension	1	
Abnormal liver/renal function	1	or 2
Bleeding tendency	1	
Labile INR	1	
Age (>65 years)	1	
CVA	1	
Drugs (e.g. aspirin) or alcohol	1	or 2
Score: 0–2 = low bleeding risk; ≥3 = high bleeding risk.		

INR, international normalized ratio; CVA, cerebrovascular accident.

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Anticoagulation after PCI

- In patients in whom anticoagulation is required post-procedure, a DOAC (apixaban 5mg bd, rivaroxaban 20mg od, edoxaban 60mg od, dabigatran 150mg bd) is preferred over warfarin.
- Triple therapy including a direct oral anticoagulant (DOAC), aspirin and a $P2Y_{12}$ inhibitor is recommended for 1 week (ESC Class I recommendation), followed by a DOAC and a single antiplatelet agent, preferably a $P2Y_{12}$ inhibitor, up to 12 months (ESC Class I recommendation) and then by a DOAC alone (see Fig. 1.11).
- In those with high bleeding risk, triple therapy is recommended for 1 week, followed by dual therapy with a DOAC and a single antiplatelet agent, preferably a $P2Y_{12}$ inhibitor, up to 6 months and then by a DOAC alone (ESC Class II recommendation).
- In those with high ischaemic risk, triple therapy is recommended for up to 1 month (ESC Class II recommendation), followed by a DOAC and a single antiplatelet agent, preferably a $P2Y_{12}$ inhibitor, up to 12 months (ESC Class II recommendation) and then by a DOAC alone.
- Following the 12-month period, anticoagulation monotherapy should be continued (ESC Class IIa recommendation).

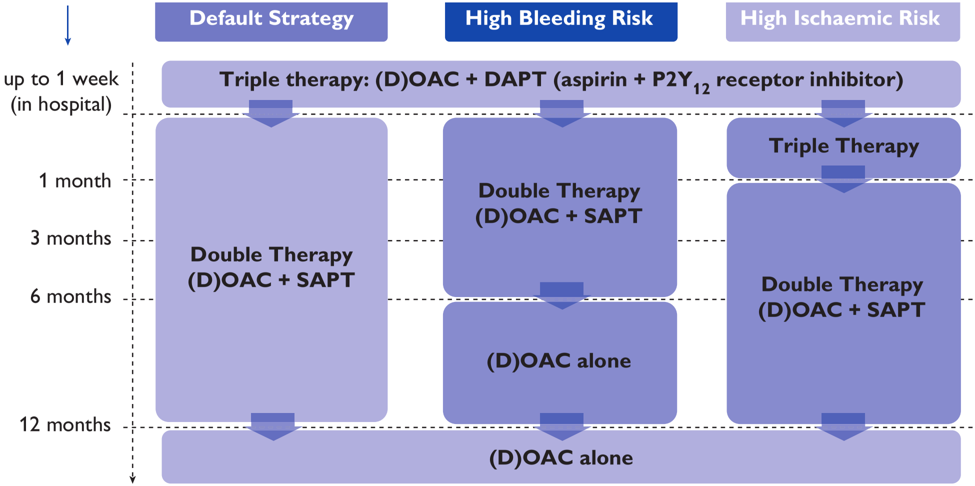
Follow-up

<1 year post-ACS or revascularization

- Patients should have at least two visits in the first year.
- In those with LV dysfunction, reassessment should be considered at 8–12 weeks.

>1 year post-ACS or revascularization

- Patients should undergo annual evaluation, including an up-to-date risk profile. An ECG should be performed on each visit to assess HR and rhythm and to look for signs of ischaemia, bloods every 2 years (risk profiling), and echocardiography every 3–5 years to assess LV function.



Default Strategy
High Bleeding Risk
High Ischaemic Risk
up to 1 week
(in hospital)
1 month
3 months
6 months
12 months
Triple therapy: (D)OAC + DAPT (aspirin + P2Y12 receptor inhibitor)
Double Therapy
(D)OAC + SAPT
Double Therapy
(D)OAC + SAPT
(D)OAC alone
Triple Therapy
Double Therapy
(D)OAC + SAPT
(D)OAC alone

Fig. 1.11 Anticoagulation strategies after percutaneous coronary intervention. DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; SAPT, single antiplatelet therapy.

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CCS: coronary artery bypass grafting

General considerations

- Decisions regarding method of revascularization should always be made in conjunction with the wider multidisciplinary team (MDT).
- *Anatomical complexity:* calculated by using the SYNTAX score (🖱 www.syntaxscore.com). This was originally devised to calculate the complexity of coronary lesions and was also found to predict cardiac events and death in patients treated with PCI. It is recommended that all patients with left main stem disease or multivessel disease undergo SYNTAX scoring.
- *Surgical mortality:* calculated by using the Society of Thoracic Surgeons (STS) risk score (🖱 https://acsdriskcalc.research.sts.org) and estimates the operative in-hospital or 30-day mortality risk.
- *Completeness of revascularization:* the aim of revascularization is to minimize ischaemia. The COURAGE trial found that there was a reduction in death and MI when stress-induced ischaemia was reduced from >10% to ≤5%—a concept which has since been confirmed in meta-analyses of nearly 90,000 patients. This also applies to high residual SYNTAX scores.

Factors favouring PCI

- Patients with severe comorbidites/reduced life expectancy.
- Patients with conditions restricting mobility and rehabilitation.
- SYNTAX score <22 (PCI = CABG in left main stem disease (see Table 1.11).
- Anatomy likely to lead to incomplete revascularization with CABG.
- Chest deformation/chest radiation complications.
- Porcelain aorta.

Factors favouring CABG

- Patients with DM.
- Patients with ↓ LVEF.
- Contraindications to DAPT.
- Recurrent in-stent restenosis.
- SYNTAX score ≥23.
- Anatomy likely to lead to incomplete revascularization with PCI.
- Severe calcification limiting the ability to expand the lesion.
- Need for concomitant cardiac surgery.

Complications

- Bleeding.
- Infection at surgical site.
- Arrhythmias.
- Pneumonia.
- Pulmonary embolism (PE).
- CVA.

Table 1.11 Recommendations for revascularization of left main stem

Left main disease	CABG	PCI
SYNTAX score 0–22	Class IA	Class IA
SYNTAX score 23–32	Class IA	Class IIa
SYNTAX score ≥33	Class IA	Class IIIB

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Data from Neumann F-J *et al*. *Eur Heart J*. 2018;**40**(2):87–165.

Early failure

- This occurs in 12% of grafts and accounts for 40–80% of cases of ischaemia post-CABG. This may be due to defects in the graft, technical errors, poor run-off of the bypassed vessel, and competitive flow.
- PCI may be required but should only be attempted in the native vessel or internal mammary graft. Any areas of anastomosis or the vein graft should be avoided due to a risk of perforation or embolization. Redo surgery may be required.

Late failure

- This may be due to progression of CAD in native vessels or graft failure, and is usually managed by revascularization, if indicated, by failure to respond to medical therapy or there is a large area of ischaemia. This is usually afforded by PCI, but redo CABG may be required.
- In general, PCI or redo CABG post-CABG has poorer outcomes, compared with those who have not had a prior CABG.
- In vein grafts, PCI may lead to embolization as the atheroma is friable, and so distal filters may help.

Ischaemia with non-obstructed coronary arteries

- Ischaemia with non-obstructed coronary arteries (INOCA) affects up to 70% of individuals undergoing invasive angiography. This is more common in men than in women.
- INOCA is usually caused by microvascular angina or coronary vasospasm which are not correctly diagnosed, leading to episodes of recurrent angina, reduced quality of life, repeated hospitalization, unnecessary coronary angiography, and adverse outcomes.

Microvascular angina

Aetiology

- This can be caused by conditions which lead to LVH such as HCM, hypertensive change, and AS, or inflammatory states (myocarditis, vasculitis).

Clinical features

- Patients typically present with exercise-related angina.

Investigations

- There is usually evidence of ischaemia on functional testing, but either normal or non-functional stenosis on coronary angiography.

Diagnosis

- Coronary flow reserve (CFR) is measured by echocardiography, MRI (myocardial perfusion imaging), or positron emission tomography (PET).
- CFR <2 is suggestive of microcirculatory dysfunction.
- Arteriolar dysregulation of the microcirculation can be diagnosed with the use of intracoronary acetylcholine. In arterioles with dysfunction of the endothelium or smooth muscle cells, rather than a vasodilatory effect, acetylcholine triggers vasoconstriction.

Prognosis

- Microvascular change can precede obstructive CAD, particularly in women.
- The presence of abnormal CFR is associated with ↑ adverse events.

Management

- In those with a negative acetylcholine test and CFR <2, β-blockers, ACEis, and statins, as well as lifestyle measures, are indicated.
- Patients with a positive response to acetylcholine testing, in the absence of epicardial vasoconstriction, should be treated as for vasospastic angina (see ➲ Vasospastic angina, pp. 58–9).

Vasospastic angina

- Patients tend to be younger and have few CV risk factors.

Clinical features

- Symptoms occur predominantly at rest, with preserved exercise tolerance.
- Episodes tend to occur at night and in the early hours of the morning.

Investigations

- Although difficult to obtain, an ECG demonstrating ST-segment elevation coinciding with symptoms supports the diagnosis.
- Ambulatory 12-lead ECG monitoring may be more likely to capture the event.
- CTCA or invasive coronary angiography should be used to rule out CAD.

Diagnosis

- Administration of intracoronary acetylcholine/ergonovine can be used to trigger vasospasm. This should be controlled with the use of nitrates. A small number of individuals may develop ventricular arrhythmias (3.2%) or bradycardia (2.7%).
- A positive test is one that causes typical symptoms, ischaemic changes on ECG, and evidence of vasoconstriction.
- Symptoms and ECG changes with no vasoconstriction may represent microvascular spasm.

Management

- DHP CCBs and long-acting nitrates are first line.

Acute coronary syndromes: overview

- ACS describes a constellation of symptoms resulting from acute myocardial ischaemia.
- Ischaemia resulting in myocyte necrosis is termed myocardial infarction.
- ACS includes the diagnosis of UA, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).
- Spontaneous coronary artery dissection and Takotsubo are important differential diagnoses to consider (see ➲ Myocardial infarction with non-obstructed coronary arteries, p. 88).

Definition

- *STEMI:* patients have chest pain and ST-segment elevation on ECG. These patients should undergo reperfusion therapy on presentation.
- *NSTEMI and UA:* patients present with chest pain associated with ST-segment changes (transient ST elevation, transient or permanent ST depression), T wave inversion/pseudonormalization/flattening. If there is biochemical evidence of myocardial injury (↑ cardiac enzymes), the condition is NSTEMI. If no myocardial injury, the condition is termed UA.
- MI may be classified into one of five types (see Box 1.9).

Box 1.9 Types of myocardial infarction

- *Type I MI:* atherosclerotic plaque disruption resulting in thrombus, leading to ↓ intracoronary blood flow
- *Type II MI:* other conditions leading to imbalance between oxygen supply and demand (e.g. arrhythmias, anaemia, respiratory failure, hypo-/hypertension)
- *Type III MI:* MI leading to death when biomarkers not available
- *Type IV MI:* related to PCI
- *Type V MI:* related to CABG

Presentation

- *Chest pain:* usually similar in nature to angina, but of greater severity and longer duration, and not relieved by S/L GTN.
- *Associated features:* these include nausea and vomiting, sweating, and shortness of breath.
- The pain may be atypical (e.g. epigastric).
- Individuals with DM and the elderly may suffer painless ('silent' infarcts) and/or atypical infarction. Presenting features include breathlessness (pulmonary oedema), syncope (dysrhythmias), acute confusional states (mania/psychosis), diabetic hyperglycaemic crises, hypotension/shock, and manifestations resembling CVA, due to sudden ↓ in cardiac output (CO) and peripheral embolization.

Conditions mimicking pain in ACS

- *Cardiac:* myo-/pericarditis, tachyarrhythmias, HF, hypertension, aortic stenosis, cardiomyopathy, coronary spasm
- *Vascular:* dissecting aortic aneurysm, PE
- *Gastrointestinal:* oesophageal reflux, spasm or rupture, perforated peptic ulcer, pancreatitis
- *Other:* trauma

Cardiac biomarkers

Creatine kinase

- Levels twice the upper limit of normal are more suggestive of myocardial damage.
- Serum levels ↑ within 4–8h and fall to normal within 3–4 days. The peak level occurs at about 24h but may be earlier (12h) and higher in patients who have had reperfusion (thrombolysis or PCI).
- Creatinine kinase (CK) levels may also be raised in patients with muscle disease or trauma, vigorous exercise, and convulsions.
- *CK-MB isoenzyme* is more specific for myocardial disease. Levels may be elevated despite a normal total CK level. However, CK-MB is also present in small quantities in other tissues (skeletal muscle, diaphragm, uterus, and prostate) and trauma or surgery may lead to false-positive results.

Cardiac troponins (troponin T, troponin I)

- High-sensitivity troponins are the gold standard in the diagnosis of ACS. They have a high negative predictive value for MI and also enable earlier detection of MI.
- Levels rise rapidly, usually within 1h if using high-sensitivity assays. Elevations >5-fold the upper limit have a high (>90%) positive predictive value in type I MI (for interpretation of troponin levels, see ➔ Fig. 1.12).

Other markers

- There are multiple other markers, but with increasing clinical availability of troponins, measurements are not recommended. These include aspartate transaminase (AST) (↑ 18–36h post-MI) and lactate dehydrogenase (LDH) (↑ 24–36h post-MI).

Other conditions leading to ↑ troponin levels

- *Cardiac causes:* arrhythmias, heart failure, cardiomyopathies, structural heart disease (e.g. aortic stenosis, myocarditis)
- *Vascular causes:* aortic dissection, pulmonary embolism
- *Critical illness:* e.g. sepsis/shock
- *Other:* chronic kidney disease, extreme endurance efforts

ACS: immediate management

- Assessment of airway, breathing, and circulation.

Airway and breathing

- Routine oxygen is not recommended if oxygen saturation is ≥90%, as hyperoxia may be harmful.
- In patients with refractory pulmonary oedema, continuous positive airway pressure (CPAP) or formal endotracheal intubation may be necessary.

Circulation

- Perform a 12-lead ECG recording within 10min.
- Attach ECG monitoring, ideally with defibrillator capacity, to the patient.
- Obtain IV access and take bloods, including clotting, haemoglobin (Hb), U&Es, liver function tests (LFTs), glucose, C-reactive protein (CRP), troponin, lipids, and glucose.

Emergency drugs

- Administer pain relief.
- In patients with NSTEMI/UA, early use of a β-blocker and S/L or IV nitrates should be considered.
- In patients with STEMI, pain relief is most commonly provided by IV morphine. Nausea and vomiting should be treated with metoclopramide (10mg IV).
- Load the patient with aspirin 300mg orally (PO) and ticagrelor 180mg PO or prasugrel 60mg PO. Patients previously taking clopidogrel should be loaded on ticagrelor, irrespective of this, unless contraindicated. In the case of NSTEMI, the second antiplatelet agent should only be given to individuals in whom the coronary anatomy is not known if the waiting time to angiography is >24h.
- Prasugrel should not be used in patients aged ≥75 years or weighing <60kg, or in those with previous CVA/TIA, as there is no clinical benefit in these individuals.
- If ticagrelor/prasugrel are contraindicated or unavailable, or in patients already on oral anticoagulation, load with clopidogrel 600mg PO.
- IV cangrelor may be considered if the patient is unable to take oral medication.

For further information on pharmacotherapy, see ➔ NSTEMI: acute management, pp. 68–9; ➔ STEMI: acute management, pp. 74–5.

Glucose control

- Glycaemic status should be evaluated in all patients, maintaining blood sugar levels at ≤11mmol/L, while avoiding hypoglycaemia. Glucose-lowering therapy should be considered in those who have glucose levels >10mmol/L. Less stringent control should be considered in those who have advanced CVD, are older, or have a greater number of comorbidities.

Further investigations

- Perform a portable CXR to assess for pulmonary oedema/pulmonary pathology.
- Echocardiography should be performed for diagnostic purposes but must not delay PCI if indicated.

Admission

- Patients with UA may be admitted to a regular ward. Patients with low-risk NSTEMI (see ➔ Table 1.13) should be admitted to the coronary care unit (CCU), with monitoring for at least 24h. Patients with intermediate- or high-risk NSTEMI should be admitted to CCU; or if too unstable, to the intensive care unit (ICU) for ≥24h observation.
- All STEMI patients should be admitted to CCU, or if too unstable to ICU.

ACS: emergency drugs

Table 1.12 shows common drugs administered during ACS.

Table 1.12 Doses of common drugs administered during ACS

Drug	Dose
Antiplatelet agents	
Aspirin	Loading dose of 300mg PO, followed by 75mg od
Clopidogrel	Loading dose of 600mg PO, followed by 75mg od
Ticagrelor	Loading dose of 180mg PO, followed by 90mg bd
Prasugrel	Loading dose of 60mg PO, followed by 10mg od
Abciximab	Bolus of 0.25mg/kg IV and 0.125mcg/kg/min infusion (max. 10mcg/min) for 12h
Tirofiban	25mcg/kg over 3min IV, followed by 0.15mcg/kg/min over 18h
Anticoagulants	
Unfractionated heparin	70–100IU/kg IV when not given with a glycoprotein (GP) IIb/IIIa inhibitor; 50–70IU/kg IV bolus with a GPIIb/IIIa inhibitor
Enoxaparin	1mg/kg s/c bd
Fondaparinux	2.5mg s/c od
Bivalirudin	100mcg/kg bolus IV, followed by a single dose of 500mcg/kg, then 1.75mg/kg/h for duration of the procedure, reduced to 250mcg/kg/h for 4–12h as necessary
Fibrinolytic agents	
Alteplase	15mg IV bolus, 0.75mg/kg IV over 30min (up to 50mg), followed by 0.5mg/kg IV over 60min (up to 35mg)
Reteplase	10U + 10U IV given at 0 and 30min
Tenecteplase	Single IV bolus based on weight

For further information on listed medications, see ➔ Chapter 17.

Cocaine-induced myocardial infarction

- Must be suspected in any young individual with chest discomfort at low risk of developing CAD.
- The cause of myocardial injury is multifactorial, including ↑ oxygen demand (↑ HR, BP, and contractility) in the context of ↓ supply caused by a combination of inappropriate vasoconstriction, enhanced platelet aggregation, and thrombus formation.
- Chest pain occurs most commonly within 12h of cocaine use. Effects can return up to 24–36h later, secondary to long-lasting active metabolites.
- Biochemical markers of cardiac injury can be misleading, as most patients will have elevated CK levels secondary to rhabdomyolysis. Therefore, troponin is essential to confirm myocardial injury.
- General management is as for acute management of ACS, including oxygen and aspirin.
- IV benzodiazepines can significantly reduce chest pain.
- GTN may be given at high doses as an IV infusion (may require doses of >10mg/h) and dose-titrated to symptoms and haemodynamic response.
- β-blockers must be avoided (e.g. propranolol). They exacerbate coronary vasoconstriction by allowing unopposed action of α-adrenergic receptors.
- If the patient fails to settle after implementing first-line measures, they should undergo immediate coronary angiography, followed by PCI if appropriate (evidence of thrombus/vessel occlusion).
- Evidence for use of thrombolysis is limited and generally associated with poor outcome secondary to hypertension-induced haemorrhagic complications.

Non-ST-segment elevation myocardial infarction: diagnosis and risk stratification

Diagnosis

Troponin

- The 2023 ESC guidelines recommend to use the 0 and 1h or 0 and 2h algorithm (see Fig. 1.12 for use of troponin in the assessment of acute chest pain).
- In patients presenting very early (within 1h of chest pain), or in those in whom troponin levels are not conclusive, a repeat troponin level should be obtained at 3h.
- As late ↑ may occur in 1% of patients, serial testing may be considered in patients in whom the clinical suspicion of ACS is high.

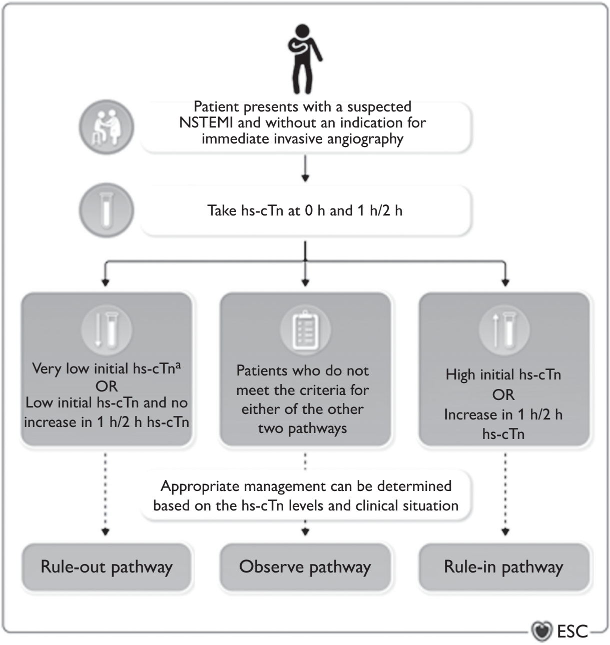
Patient presents with a suspected NSTEMI and without an indication for immediate invasive angiography
Take hs-cTn at 0 h and 1 h/2 h
Very low initial hs-cTn[a] OR Low initial hs-cTn and no increase in 1 h/2 h hs-cTn
Patients who do not meet the criteria for either of the other two pathways
High initial hs-cTn OR Increase in 1 h/2 h hs-cTn
Appropriate management can be determined based on the hs-cTn levels and clinical situation
Rule-out pathway
Observe pathway
Rule-in pathway
ESC

Fig. 1.12 Management algorithm for acute chest pain.

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GRACE risk score

- The GRACE 2.0 risk score combines variables of age, HR, BP, creatinine, Killip class on presentation, cardiac arrest, raised cardiac biomarkers, and ST changes in order to calculate a score of mortality in hospital, and at 6 months, 1 year, and 3 years (🖱 www.outcomes-umassmed.org/grace/acs_risk2/index.html).
- If the Killip class or creatinine are not available, this can be substituted with renal failure and diuretics, respectively.

Timing of intervention

- Timing of intervention is determined by the risk of the individual (see Table 1.13).

Table 1.13 Classification of risk in NSTEMI

Very high risk	Cardiac arrest Haemodynamic instability/shock Ongoing chest pain refractory to treatment Acute heart failure Mechanical complications Life-threatening arrhythmias Dynamic ST changes, including intermittent ST-segment elevation
High risk	Troponin levels compatible with MI Dynamic ST and T wave changes Transient ST-segment elevation GRACE score >140
Intermediate risk	LVEF <40% Renal failure (EGFR<60mL/min/1.73m^2) DM Prior PCI/CABG Early post-infarction angina GRACE score >109 but <140
Low risk	Characteristics not listed above

- Very high risk should undergo angiography within 2h, high risk within 24h, and intermediate within 72h, and low risk should undergo non-invasive testing if appropriate.
- In patients with no ischaemic changes and negative troponin levels, stress imaging (echocardiography/MRI/nuclear imaging; see ➲ Dobutamine stress echocardiography, pp. 516–17; CMR: coronary artery disease, pp. 552–3; Myocardial perfusion scintigraphy, pp. 562–3) may be considered after a few hours or after discharge.
- In patients with low or intermediate probability, CTCA has a high negative predictive value to exclude ACS.

NSTEMI: acute management

For further information on listed medications, see ➔ Chapter 17.

Anticoagulation

- This should be given at the time of diagnosis, weighing up ischaemia vs bleeding risks.
- There are multiple options for acute anticoagulation, including the following.

Unfractionated heparin

- This is recommended as the anticoagulant of choice for PCI.
- UFH is administered IV with a bolus of 60–70IU/kg, up to 5000IU. This should be followed by an infusion of 12–15IU/kg/h, up to a maximum of 1000IU/h.
- This is a factor Xa and thrombin inhibitor.
- The dose does not need to be adjusted in renal failure.

Fondaparinux

- This is a factor Xa inhibitor, which is often given during a conservative treatment phase.
- The recommended dose in NSTEMI is 2.5mg/day s/c.
- Fondaparinux is not recommended if the glomerular filtration rate (GFR) is <20mL/min/1.73m^2.
- As catheter thrombus formation may be an issue, during PCI, a standard bolus of UFH should additionally be given if fondaparinux is used.

Low-molecular weight heparin

- The most commonly used low-molecular weight heparin (LMWH) is enoxaparin 1mg/kg bd. This is a factor Xa and thrombin inhibitor.
- This should be considered an anticoagulant for PCI if the patient has already been treated with enoxaparin.
- The dose should be adjusted to od in stage 4 CKD and is not advised in those with stage 5 CKD.
- No additional enoxaparin is recommended during PCI if the last dose was <8h ago. A further 0.3mg/kg bolus is recommended if the last dose was >8h ago.

Antiplatelets

Aspirin

- Aspirin is a thromboxane A2 inhibitor, which should be administered as a loading dose of 300mg.

Clopidogrel vs ticagrelor

- Clopidogrel and ticagrelor are $P2Y_{12}$ inhibitors.
- The PLATO study compared patients with moderate- to high-risk NSTEMI/STEMI given loading with 300–600mg clopidogrel (75mg maintenance) to those given 180mg ticagrelor (90mg bd maintenance). This showed that in the NSTEMI arm, the composite end point of death from CV causes, MI, or stroke was significantly reduced in those patients receiving ticagrelor. There was no difference in life-threatening or fatal bleeds. Therefore, ticagrelor is preferred over clopidogrel.

Prasugrel

- Based on the findings of the TRITON-TIMI 38 trial, prasugrel should be considered in patients with stent thrombosis despite being on clopidogrel. This study, however, showed no benefit in patients aged ≥75 years, those who weigh <60kg, and those with previous TIA/CVA.
- The ACCOAST trial and SCAAR registry both demonstrated that there was no ischaemic benefit to pretreatment of NSTEMI patients with a $P2Y_{12}$ inhibitor, and in fact there was ↑ risk of bleeding events.
- The ISAR-REACT 5 study demonstrated that in individuals with ACS randomly assigned to deferred loading (after knowledge of the coronary anatomy) with prasugrel or pretreatment with ticagrelor, the incidence of death, MI, or CVA was significantly lower in those who received prasugrel. There was no difference in bleeding rates between the two groups.
- Therefore, routine pretreatment with a $P2Y_{12}$ inhibitor is not recommended if an early invasive strategy is planned but should be considered if angiography is likely to be delayed. Prasugrel is preferred to ticagrelor in those proceeding to PCI.

Cangrelor

- Cangrelor is an IV $P2Y_{12}$ inhibitor. This may be considered if the patient is unable to take oral medication.

Novel oral anticoagulants

- In the ATLAS ACS 2-TIMI 51 study, rivaroxaban 2.5mg and 5mg bd doses were compared to placebo post-NSTEMI and STEMI. The 2.5mg bd dose conferred a lower rate of CV death and reduced rates of bleeding, compared with the higher dose of rivaroxaban.
- These findings have led to the European Medicines Agency's approval of rivaroxaban 2.5mg bd, in combination with aspirin and clopidogrel (not ticagrelor/prasugrel), for both NSTEMI and STEMI patients if ticagrelor/prasugrel are not available and the patient has low bleeding risk and high ischaemia risk.

Post-PCI management

- *Management of TR band and femoral compression device* (see ➔ Vascular closure devices, pp. 584–5).

Coronary artery bypass graft

- CABG may be considered in individuals with haemodynamic instability, ongoing ischaemia, or high-risk CAD if not considered suitable for PCI.
- CABG in stabilized patients may offer complete revascularization in patients with multivessel disease. For factors favouring CABG, see ➔ Factors favouring CABG, p. 56. In cases of less urgent CABG, platelet therapy should be interrupted (aspirin should continue): 3 days for ticagrelor; 5 days for clopidogrel; and 7 days for prasugrel. DAPT should be continued post-operatively for 12 months.

NSTEMI: longer-term management

Risk factor management

- *CAD:* risk factor modification (see ➔ CAD: risk factor modification, pp. 14–15).
- *Hypertension:* investigation and management (see ➔ Hypertension: investigation, p. 34; Hypertension: management, pp. 36–9).
- *DM:* management in CVD (see ➔ DM: management in atherosclerotic CVD, pp. 18–21).
- *Dyslipidaemias:* guidelines and targets (see ➔ Dyslipidaemias: guidelines and targets, p. 26).

Medications

Dual antiplatelet therapy

- In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor, on top of aspirin, is recommended for 12 months (3–6 months may be considered in those who are not at high ischaemic risk), unless there are contraindications such as excessive risk of bleeding (see Table 1.10) (ESC Class I recommendation); if high bleeding risk, this may be reduced to 1 month (ESC Class IIb recommendation).
- If a patient is taking an oral anticoagulant, then they should be managed as per anticoagulation guidelines post-intervention for CCS (see ➔ Fig. 1.11), switching from ticagrelor/prasugrel to clopidogrel, as these are not licensed for use with an oral anticoagulant.
- Fig. 1.13 shows how to switch between antiplatelet therapies in acute and chronic settings.
- A proton pump inhibitor should be considered in those at high risk of gastrointestinal (GI) bleeding requiring DAPT.

β-blockers

- β-blockers are recommended for all ACS patients with LVEF ≤40%, including those without HF symptoms, but should be considered for all ACS patients.

Angiotensin-converting enzyme inhibitors

- ACEis are recommended for those with HF symptoms, LVEF ≤40%, DM, hypertension, or CKD, but should be considered for all ACS patients.

Mineralocorticoid receptor antagonists

- Mineralocorticoid receptor antagonists (MRAs) are recommended in those with LVEF ≤40% and HF or diabetes.

Implantable cardioverter–defibrillator therapy

- Those with LVEF <40% should be re-evaluated at 6–12 weeks to assess the need for an implantable cardioverter–defibrillator (ICD).
- If the patient has symptomatic HF (NYHA classes II–III) with LVEF ≤35% following 3 months of OMT, an ICD may be indicated. Cardiac resynchronization therapy with defibrillator capability (CRT-D) may be more appropriate if the QRS interval is >130ms.

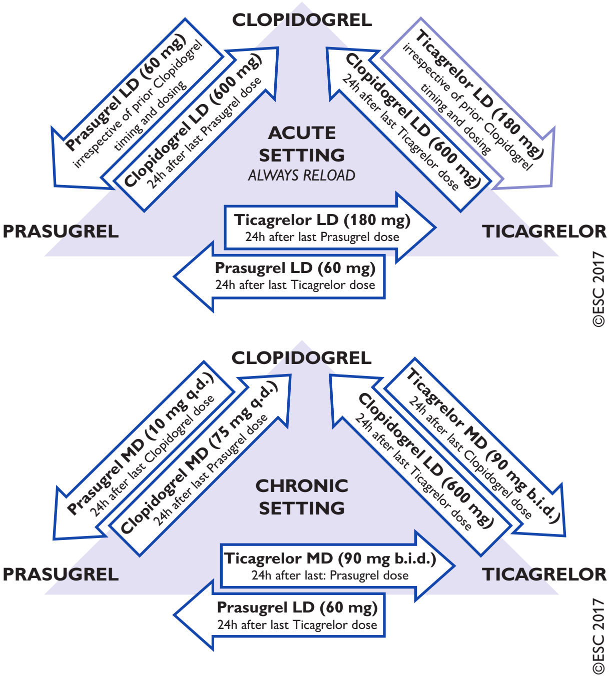
CLOPIDOGREL
Prasugrel LD (60 mg)
irrespective of prior Clopidogrel timing and dosing
Clopidogrel LD (600 mg)
24h after last Prasugrel dose
Ticagrelor LD (180 mg)
irrespective of prior Clopidogrel timing and dosing
Clopidogrel LD (600 mg)
24h after last Ticagrelor dose
ACUTE SETTING
ALWAYS RELOAD
PRASUGREL
TICAGRELOR
Ticagrelor LD (180 mg)
24h after last Prasugrel dose
Prasugrel LD (60 mg)
24h after last Ticagrelor dose
©ESC 2017
CLOPIDOGREL
Prasugrel MD (10 mg q.d.)
24h after last Clopidogrel dose
Clopidogrel MD (75 mg q.d.)
24h after last Prasugrel dose
Ticagrelor MD (90 mg b.i.d.)
24h after last Clopidogrel dose
Clopidogrel LD (600 mg)
24h after last Ticagrelor dose
CHRONIC SETTING
PRASUGREL
TICAGRELOR
Ticagrelor MD (90 mg b.i.d.)
24h after last: Prasugrel dose
Prasugrel LD (60 mg)
24h after last Ticagrelor dose
©ESC 2017

Fig. 1.13 Switching between antiplatelet therapies. bid, twice daily; qd, once daily.

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ST-segment elevation myocardial infarction: overview

Epidemiology

- Data from European registries estimate the incidence of STEMI to be around 60/100,000 people per year.
- STEMI occurs more frequently in younger individuals compared with those with NSTEMI, and most commonly in men.

Diagnosis

- STEMI is diagnosed based on typical symptoms of MI, known history of CAD, CV risk factors, and ECG findings. Biochemical markers may not be immediately available on presentation but can assist in reconfirming the diagnosis.

ECG findings

- ST-segment elevation at the J point in at least two contiguous leads of ≥2.5mm in men aged <40 years and ≥2mm in men aged ≥40 years, or ≥1.5mm in women in leads V2–3 and/or ≥1mm in other leads (in the absence of LBBB and LVH).
- ST-segment depression of ≥0.5mm in leads V1–3 suggests posterior MI. A diagnosis of posterior MI is confirmed by ≥0.5mm elevation (≥1mm in men aged 40 years) in posterior leads V7–9.
- Patients with a suspected ongoing MI and LBBB should also be managed as STEMI. The modified Sgarbossa criteria may be used to identify MI in the presence of LBBB.
- Localization of the infarct is shown in Box 1.10.
- Conditions that may mimic ECG changes of an STEMI are listed in Box 1.11.

Modified Sgarbossa criteria*

- ≥1 lead with ≥1mm of concordant ST-segment elevation.
- ≥ 1 lead (V1–3) with ≥1mm of concordant ST-segment depression.
- ≥1 lead anywhere with ≥1mm of ST-segment elevation and proportionally excessive discordant ST-segment elevation, as defined by ≥25% of the depth of the preceding S wave.

* MI if any criteria are met.

Other clinical scenarios which may require PCI

- Left main coronary obstruction ST-segment depression of ≥1mm in eight or more surface leads, together with ST-segment elevation in lead aVR or V1, may suggest left main coronary artery obstruction and therefore a need for urgent PCI.
- A primary PCI strategy should also be considered in patients with persistent ischaemic symptoms and right bundle branch block (RBBB).
- In patients with ongoing ischaemic symptoms in the absence of ST-segment elevation and ≥1 of the following: haemodynamic instability/cardiogenic shock, electrical instability, recurrent ST/T wave changes, refractory chest pain, acute HF, and mechanical complications of MI.

Prognosis

- Although PCI, developments in antithrombotic medication, and secondary prevention strategies have led to ↓ short-term, as well as long-term, mortality, 1-year mortality remains ~10%.

Box 1.10 Localization of infarcts from ECG changes

Septal	ST-segment elevation and/or Q waves in V1– V2
Anterior	ST-segment elevation and/or Q waves in V3–V4
Lateral	ST-segment elevation and/or Q waves in V5–V6 and T wave inversion/ST-segment elevation/Q waves in I and aVL
Inferior	ST-segment elevation and/or Q waves in II, III, and aVF
True posterior	ST-segment elevation in V2–V9, with ST-segment depression in V1–V2; T waves remain upright in V1–V2
Right ventricular infarction	ST-segment elevation in right precordial leads (V3R–V4R); this may only be present in early hours of infarction (NB persisting elevation after 1 month suggests a left ventricular thrombus)

Box 1.11 Conditions that may mimic ECG changes of STEMI

- Left/right ventricular hypertrophy
- Left bundle branch block
- Wolff–Parkinson–White syndrome
- Myocarditis/pericarditis
- Cardiomyopathy
- Pulmonary embolus
- Intracranial haemorrhage
- Hyperkalaemia

STEMI: acute management

- Primary percutaneous coronary intervention (PPCI) is the current gold standard reperfusion strategy for treatment of STEMI.

PPCI

Optimal timing

- PPCI should be performed by an experienced operator in a centre that offers a PPCI service 24/7, within 120min from the diagnosis of an STEMI, ideally aiming for reperfusion (wire crossing) at ≤60min from diagnosis or ≤90min if the patient has been transferred from a non-PCI centre.
- If STEMI is confirmed in a non-PCI centre, the patient must be transferred to the nearest PCI centre without delay, with the aim of a door-in, door-out time of ≤30min.

Preferred options for intervention

- The radial route is preferred due to reduced vascular complications, bleeding, and transfusion rates, compared with the femoral approach.
- Anticoagulation (UFH, enoxaparin) should be administered to the patient. Patients already taking anticoagulation should receive parenteral anticoagulation, regardless of their last dose of oral anticoagulant. Bivalirudin is indicated in the case of heparin-induced thrombocytopenia.
- Thrombus aspiration is not indicated due to a likely ↑ risk of CVA; however, a GPIIb/IIIa antagonist, such as abciximab, may be given if there is evidence of large thrombus burden or slow flow or no reflow. This should be avoided in patients taking oral anticoagulation.
- Stenting with new-generation drug-eluting stent (DES) is preferable to balloon angioplasty and bare metal stents, largely due to the reduction in reintervention rates and mortality.

CABG

- If PPCI cannot be performed, with ongoing ischaemia and large areas of vulnerable myocardium, an urgent CABG should be considered.
- CABG/surgery should also be considered in cases of high-risk coronary anatomy (e.g. left main stem/ostial left anterior descending stenosis) and mechanical complications (e.g. acute MR, ventricular septal defect (VSD)).
- In cases of less urgent CABG, platelet therapy should be interrupted (aspirin should be continued)—3 days for ticagrelor, 5 days for clopidogrel, and 7 days for prasugrel. DAPT should be continued post-operatively for 12 months.

Other scenarios where PPCI may also be considered

- If >12h from the time of onset, PPCI is indicated in the presence of ongoing ischaemic symptoms, life-threatening arrhythmias, or haemodynamic instability.
- In individuals presenting 12–48h after symptom onset, a routine PPCI strategy is appropriate; however, if >48h have passed from symptom onset, and the patient is pain-free, there is no indication to perform PCI. In these cases, the patient can be assessed by using a non-invasive test in order to assess ischaemia burden/viability.

Management of multiple stenoses

- Studies (PRAMI, CULPRIT, DANAMI-3-PRIMULTI, and Compare-Acute) have shown that not only revascularization of the culprit lesion, but also preventative PCI in non-infarct arteries has reduced the need for reintervention.
- In the recent COMPLETE study, patients were randomized following successful culprit lesion revascularization to revascularization of non-culprit lesions in hospital or following discharge vs no further revascularization. The composite primary outcome was a composite of MI and CV death. The secondary outcome was a composite of ischaemia-driven revascularization, MI, and CV death. For both outcomes, revascularization was superior, irrespective of timing of non-culprit revascularization.
- Complete revascularization is recommended either during the index procedure or within 45 days for STEMI, and should be considered in NSTEMI.
- PCI of non-infarct-related vessels is not recommended if the patient is in cardiogenic shock, and staged complete revascularization should be considered.

STEMI and cardiac arrest

- PCI should be considered in patients with STEMI and cardiac arrest.
- Urgent angiography within 2h should be performed where there is a high suspicion of ongoing ischaemia (chest pain before arrest, known CAD, and abnormal ECG).
- In patients without ST-segment elevation, further investigations should be undertaken before coronary angiography. These decisions should also take into account the likelihood of neurological recovery (unwitnessed arrest, late arrival of pre-hospital team, downtime of >20min).
- Temperature control, with prevention of fever, is recommended for those who remain unresponsive post-cardiac arrest.

STEMI: thrombolysis

- Thrombolysis is indicated when PCI cannot be performed within ≤120min of STEMI diagnosis and if <12h from symptom onset.
- The main complication with thrombolysis is intracranial haemorrhage. This can occur in up to 1% and major non-cerebral bleeds in 4–13%. Box 1.12 lists the absolute contraindications to thrombolysis.
- Efficacy diminishes with time; therefore, thrombolytic drugs should ideally be administered ≤10min from STEMI diagnosis.
- The agent of choice should be fibrin-specific (e.g. tenecteplase, alteplase, or reteplase). Box 1.13 lists the complications of thrombolysis.
- (See ➲ ACS: emergency drugs, p. 64.)
- The patient should be additionally loaded on aspirin and clopidogrel.
- Anticoagulation is recommended in patients who have undergone fibrinolysis until PCI or for the duration of admission (up to 8 days).
- Patients should be routinely transferred to a PCI centre within 60–90min, with an aim to perform PCI within 2–24h.
- Emergency PCI should be performed immediately if, following fibrinolysis, the patient has HF/shock or fibrinolysis fails (<50% ST-segment resolution at 60–90min) or if there is evidence of haemodynamic or electrical instability or worsening ischaemia.

Box 1.12 Contraindications to thrombolysis

- Previous intracranial haemorrhage
- Cerebrovascular accident within 6 months
- Recent major trauma/head injury/surgery (<1 month)
- Central nervous system tumours/arteriovenous malformations
- Gastrointestinal bleeding (<1 month)
- Known bleeding disorder
- Aortic dissection
- Non-compressible puncture in the past 24h (e.g. lumbar puncture/liver biopsy)

Box 1.13 Complications of thrombolysis

- Bleeding
- Hypotension (more common with streptokinase)
- Allergic reaction (more common with streptokinase)
- Intracranial haemorrhage
- Reperfusion arrhythmias (most commonly a short, self-limiting run of idioventricular rhythm) may occur, as the metabolites are washed out of the ischaemia tissue (for management, see ➲ Ventricular tachyarrhythmias post-MI, p. 86)
- Systemic embolization may occur from lysis of thrombus within the left atrium, left ventricle, or aortic aneurysm

STEMI: post-PPCI management

- All patients should be admitted to CCU or, if too unstable, to ICU.
- All patients should have cardiac monitoring for at least 24h, with duration governed by the clinical picture.
- Glycaemic status should be evaluated in all patients, maintaining blood sugar levels at ≤11mmol/L while avoiding hypoglycaemia. Glucose-lowering therapy should be considered in those who have glucose levels >10mmol/L. Less stringent control should be considered in those who have advanced CVD, are older, and have a greater number of comorbidities.
- For management of PCI access site, see ➔ Vascular closure devices, pp. 584–5.
- Early ambulation is advised for all patients.

STEMI: risk stratification

- Discharge is determined by risk stratification. This may be calculated by using scoring systems such as the Zwolle PPCI index (see Table 1.14).
- The Zwolle score uses six clinical variables to identify low-risk PPCI patients (score ≤3) who can be safely discharged as early as 48h.

Table 1.14 Zwolle PPCI index

Criteria	Score
Killip class	
1	0
2	4
3–4	9
TIMI flow post-PCI	
3	0
2	1
0–1	2
Age	
<60 years	0
≥60 years	2
Triple-vessel disease	
No	0
Yes	1
Anterior infarction	
No	0
Yes	1
Ischaemia time >4h	
No	0
Yes	1
TOTAL	**/16**

Risk score 0–1 = RR 0.03 of death by 30 days; 2 = RR 0.09; 3 = RR 1.04; 4 = RR 1.40; 5 = RR 2.48'; 6 = RR 2.52; 7 = RR 5.99; ≥8 = RR 32.1.

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STEMI: longer-term management

Risk factor management

- *CAD:* risk factor modification (see ➔ CAD: risk factor modification, pp. 14–15).
- *Hypertension:* investigations and management (see ➔ Hypertension: investigations, p. 34; Hypertension: management, pp. 36–9).
- *DM:* management in CVD (see ➔ DM: management in atherosclerotic cardiovascular disease, pp. 18–21).
- *Dyslipidaemias:* guidelines and targets (see ➔ Dyslipidaemias: guidelines and targets, p. 26).

Medications

For further information on listed medications, see ➔ Chapter 17.

Dual antiplatelet therapy

- In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor, on top of aspirin, is recommended for 12 months (3–6 months may be considered in those who are not at high ischaemic risk), unless there are contraindications such as excessive risk of bleeding (see Table 1.10) (ESC Class I recommendation); if high bleeding risk, this may be reduced to 1 month (ESC Class IIb recommendation).
- If a patient is taking an oral anticoagulant, then they should be managed as per anticoagulation guidelines post-intervention for CCS (see ➔ CCS: management of antiplatelets and anticoagulation, pp. 52–3), switching from ticagrelor/prasugrel to clopidogrel, as these are not licensed for use with an oral anticoagulant.

(See Fig. 1.13 to switch between antiplatelet therapies in the acute and chronic settings.)

β-blockers

- β-blockers are recommended for all ACS patients with LVEF ≤40%, including those without HF symptoms, but should be considered for all ACS patients.

Angiotensin-converting enzyme inhibitors

- ACEis are recommended for those with HF symptoms, LVEF ≤40%, DM, hypertension, or CKD but should be considered for all ACS patients.

Mineralocorticoid receptor antagonists

- MRAs are recommended for those with LVEF ≤40% and HF or DM.

Implantable cardioverter–defibrillator therapy

- Those with LVEF <40% should be re-evaluated at 6–12 weeks to assess the need for an ICD.
- If the patient has symptomatic HF (NYHA classes II–III), with LVEF ≤35% following 3 months of OMT, an ICD may be indicated. CRT-D may be more appropriate if the QRS interval is >130ms.

Complications post-MI: overview

Complications are encountered more commonly in patients post-STEMI but can also be found in NSTEMI patients. These include:

- Continuing chest pain
- New systolic murmur (VSD, acute MR)
- Pump failure (cardiac failure, cardiogenic shock, right ventricular (RV) infarction, pseudoaneurysm, and free wall rupture)
- Arrhythmias (ventricular tachycardia (VT), AV block, ectopics, and bradycardia)
- Thrombosis
- Fever.

Complications post-MI: further chest pain

- Chest pain post-MI is not necessarily angina. Careful history is needed to characterize the pain.

Musculoskeletal pain

- A bruised sensation and musculoskeletal pain are common in the first 24–48h, especially in patients who have received cardiopulmonary resuscitation (CPR) or repeated shocks. This is managed with regular analgesia.

Angina/ischaemia

- Patients with angina, ischaemia, or infarction early post-PCI should ideally undergo immediate coronary angiography and, if indicated, PCI/CABG.

Pericarditis

- This presents as sharp chest pain which may be related to posture and respiration. A pericardial rub may be heard on examination. Echocardiography should be performed early in order to diagnose any associated pericardial effusions. This is managed with anti-inflammatory therapy (see ➔ Post infection pericarditis, p. 309).

Pericardial effusion

- See ➔ Pericardial effusion with or without tamponade, pp. 298–9.

Pulmonary thromboembolism

- This can occur in cases of prolonged bed rest. Routine use of prophylactic LMWH, combined with early mobilization, has reduced the incidence of PE.

Complications post-MI: new systolic murmur

Ventricular septal defect post-MI

- This is classically seen 24h (highest risk) to 10 days post-MI.

Basic pathology

- A VSD results from a transmural infarct. Anterior infarction is associated with apical VSD, and inferior MI with basal VSD.

Clinical features

- Patients present with rapid deterioration and a harsh pansystolic murmur (maximal at the lower left sternal edge), hypotension, and pulmonary oedema. The absence of a murmur in the context of a low-output state does not rule out a VSD.

Diagnosis

- *ECG:* to assess for arrhythmias/ischaemic changes.
- *Portable CXR:* to assess the degree of pulmonary oedema.
- *Echocardiography:* the defect may be visualized on echocardiography; colour flow Doppler shows the presence of left-to-right shunt.
- *Pulmonary artery (PA) catheter (especially in absence of conclusive/inconclusive echocardiographic results)*: a step-up in oxygen saturation from the right atrium (RA) to the right ventricle (RV) confirms the presence of a shunt. The degree of the shunt can be calculated by:

$$Q_p : Q_s = \frac{(\text{Art sat - RA sat})}{(\text{Art sat - PA sat})} \text{ where } \frac{Q_P = \text{pulmonary blood flow}}{Q_s = \text{systernic blood flow}}$$

$$\text{and Art} = \text{arterial and sat} = \text{saturation}$$

Management

- The patient should be stabilized until a definitive surgical repair can take place; admit to high dependency unit (HDU)/ICU (see ➔ Management of acute heart failure, pp. 108–11).
- Give oxygen; if worsening hypoxia/acidosis on arterial blood gas (ABG), consider CPAP/bilevel ventilation/intubation.
- Invasive monitoring is required (pulmonary artery (PA) catheter and arterial line) to dictate haemodynamic management.
- Right atrial (RA) pressure and pulmonary capillary wedge pressure (PCWP) dictate fluid administration or diuretic use. CO, mean arterial pressure, and arterial resistance determine the need for vasodilator therapy.
- If SBP >100mmHg, cautious use of vasodilator therapy, generally with nitroprusside—will lower systemic vascular resistance and reduce the magnitude of the shunt. Nitrates will cause venodilatation and ↑ the shunt, and should be avoided.
- Inotropes should be given if severely hypotensive (initially dobutamine, but adrenaline may be required, depending on haemodynamic response). Increasing systemic pressure will worsen the shunt.
- In most cases, an intra-aortic balloon pump (IABP) should be inserted rapidly for counterpulsation (see ➔ Intra-aortic balloon pump, p. 616).

- If the patient has been weaned off pharmacological and/or mechanical support, it may be possible to postpone surgery for 2–4 weeks to allow for some level of infarct healing. Patients should ideally undergo catheterization prior to surgical repair to ensure culprit vessel(s) are grafted.

Acute mitral regurgitation post-MI

- MR is seen between 2 and 7 days post-MI.

Basic pathology

- There are three mechanisms of MR, including mitral annular dilatation secondary to LV dilatation, ischaemic papillary muscle dysfunction, and partial rupture of the papillary muscle.
- Rupture is more commonly associated with infarct in the right/circumflex artery territory (posteromedial papillary muscle). Complete papillary muscle rupture is fatal. Papillary muscle rupture leads to sudden elevation of left atrial (LA) pressure, which subsequently leads to pulmonary congestion and sudden deterioration.

Clinical features

- Patients present with acute breathlessness.
- Clinical signs are different to those seen in the chronic setting, as the left atrium (LA) is non-dilated and relatively non-compliant. Patients may be tachycardic and hypotensive, with clinical evidence of pulmonary oedema and a pansystolic murmur of MR.
- Later in the illness, due to sustained high LA and pulmonary venous pressures, right HF develops.
- On clinical examination, the murmur may be quiet. 'Silent MR' is quite frequent and must be suspected in any post-MI patient with unexplained haemodynamic deterioration.

Diagnosis

- *ECG:* to assess for arrhythmias/ischaemic changes.
- *Portable CXR:* to assess the degree of pulmonary oedema.
- *Echocardiography:* for diagnosis and quantification of MR.
- *Transoesophageal echocardiography (TOE):* can provide specific information about the aetiology of valve dysfunction, including papillary muscle rupture and mitral valve (MV) leaflet (anterior and posterior) structural abnormalities. This information is vital for a decision regarding definitive management.

Management

- In patients with cardiogenic shock and pulmonary oedema with severe MR, emergency surgery is required and admit to HDU/ICU.
- Give oxygen; if worsening hypoxia/acidosis on ABG, consider CPAP/bilevel ventilation/intubation.
- Consider inotropic support (e.g. dobutamine).
- An IABP will help ↓ left ventricular end-diastolic pressure (LVEDP) and ↑ coronary blood flow (see ➲ Intra-aortic balloon pump, p. 616).

Complications post-MI: pump failure

- Usually due to direct myocardial damage but can also be caused by mechanical complications (e.g. VSD/acute MR) or arrhythmias.

Acute heart failure

- See ➔ Management of acute heart failure, pp. 108–11.

Cardiogenic shock

- Occurs in 6–10% of all STEMI cases; 50% in-hospital mortality rate.

Basic pathology

- Usually due to extensive LV damage but may occur in RV infarcts.

Diagnosis

- Defined as persistent hypotension (SBP ≤90mmHg) despite adequate filling status, with signs of hypoperfusion.
- Shock is defined as the need for inotropes and/or mechanical support to maintain BP >90mmHg.
- Haemodynamically, this equates to a cardiac index of ≤2.2L/min/m^2, wedge pressure of ≥18mmHg, and diuresis usually of <20mL/h.

Clinical features

- Patients present with ↓ BP, as well as with features of ↓ CO (e.g. oliguria, cool peripheries, confusion, pulmonary oedema).

Diagnosis

- *Echocardiography:* to assess LV function and cardiac structure.
- *Haemodynamic assessment:* to ensure adequate monitoring and access; may include central venous lines, Swan–Ganz, arterial line insertion, urinary catheter.
- *Angiography:* with a view to performing PCI or CABG if appropriate.

Management

- Admit to HDU/ICU.
- Give oxygen; if worsening hypoxia/acidosis on ABG, consider CPAP/bilevel ventilation/intubation.
- The first step in management is to try and identify reversible causes. This may include arrhythmias, electrolyte abnormalities, hypovolaemia, and drug-induced hypotension.
- In cases of mechanical complications, specific treatments related to the underlying condition should be initiated.
- In STEMI patients, immediate reperfusion is recommended.
- Aim to improve haemodynamic status, achieving SBP ~90mmHg. Inotropic support should, in the first instance, be with dobutamine (see ➔ Inotropes and vasopressors, pp. 792–3). Levosimendan is an option for patients on β-blockers, as its effect is independent of β-adrenergic stimulation.
- Short-term mechanical support may be considered to stabilize the patient and allow recovery of myocardial function, or as a bridge to LV assist devices (LVADs)/cardiac transplant (see ➔ Haemodynamic support devices, pp. 616–17).
- IABP therapy is not recommended in STEMI patients but should be considered in those with mechanical complications (e.g. MR/VSD).

Right ventricular infarction

- Commonly occurs in inferior STEMI. Important to distinguish RV infarct from shock due to LV dysfunction, as management differs.

Basic pathology

- This results in ↑ right-sided pressures (RA, RV end-diastolic pressure (RVEDP)) and ↓ left-sided pressures (BP and CO).

Clinical features

- Signs of right HF (↑ jugular venous pressure (JCP)) without pulmonary oedema in the context of a low-output state (↓ BP).

Diagnosis

- *ECG:* in those with inferior STEMI, >1mm ST-segment elevation in any one of leads V4R–V6R is highly sensitive and specific for RV infarction. Patients may develop ventricular arrhythmias and AV block.
- *Echocardiography:* RV dilatation and wall motion abnormalities.

Management

Aim to maintain a high RV preload

- Initially give 1–2L of IV fluid loading.
- Avoid use of nitrates, diuretics, and ACEis, as they reduce preload and can worsen hypotension.
- In patients requiring pacing, AV synchrony must be maintained to ensure maximal CO (atrial and ventricular wires).
- Cardiovert any arrhythmias, especially atrial arrhythmias, as the atrial contribution to filling becomes very important in this setting.

Reduce afterload

- This is particularly important if there is concomitant LV dysfunction.
- Consider insertion of an IABP.
- Arterial vasodilators can be used with caution.
- Inotropic support should ideally be avoided and used if all other measures fail to restore haemodynamic status.
- Reperfusion of the right coronary artery (RCA) has been demonstrated to improve RV function and reduce mortality.

Pseudoaneurysm and free wall rupture

- Usually presents with CV collapse and electromechanical dissociation (electrical activity continues, but CO is lost).
- About 25% present subacutely due to thrombus/adhesion sealing the defect.
- Can mimic reinfarction as pain returns and ST-segment elevation. Often there is sudden haemodynamic ↓ due to cardiac tamponade.
- Echocardiography may diagnose subacute cases (effusion ± tamponade). The most common finding is an echo-dense mass, consistent with a clot, in the pericardial space.
- Patient stabilization is similar to that for cardiogenic shock (see ➔ Cardiogenic shock, p. 84).
- Immediate surgical discussion, with a view to repair, is required.

Complications post-MI: arrhythmias

For detailed management of brady- and tachyarrhythmias, see ➔ Bradyarrhythmias, p. 844; Tachyarrhythmias, pp. 840–1.)

Ventricular tachyarrhythmias post-MI

Accelerated idioventricular rhythm

- Common in those with early reperfusion in first 48h. Usually self-limiting, with no haemodynamic effects. Does not require antiarrhythmic therapy.

Ventricular ectopics

- These are common and not related to the incidence of sustained VT/ventricular fibrillation (VF). They are generally treated conservatively and rarely require medical therapy.

Sustained/haemodynamically significant ventricular tachycardia

- Occurs in 3% of all MIs.
- Aim to correct acid–base and electrolyte abnormalities (aim for potassium (K^+) >4.0mmol/L and magnesium (Mg^{2+}) >1.0mmol/L).
- Non-sustained VT and haemodynamically stable VT can be treated with β-blockers, amiodarone ± lidocaine.
- Direct current cardioversion (DCCV) is indicated for haemodynamic instability.
- For incessant VT despite therapy, consider overdrive pacing.
- Pulseless VT and VF should be managed as per advanced life support (ALS) guidelines (see ➔ Treatment of shockable rhythms (ventricular fibrillation/pulseless ventricular tachycardia), pp. 826–7).

Atrial tachyarrhythmias post-MI

- Includes supraventricular tachycardia (SVT), atrial fibrillation (AF), and atrial flutter.
- AF occurs in 10–20% of STEMIs and can lead to ↑ risk of CVA and in-hospital mortality. In cases of AF leading to HF, it should be treated with rate control (β-blockers, CCBs) or rhythm control (amiodarone). Anticoagulants are indicated.
- Other SVTs are rare and usually self-limiting. They may respond to carotid sinus pressure, adenosine, or β-blockers.
- DCCV is indicated for haemodynamic instability.

Bradyarrhythmias

- Sinus bradycardia is common within the first few hours of STEMI (9–25% of STEMI patients). Treatment is required if this causes haemodynamic instability.
- AV block occurs in around 7%. This leads to higher mortality (related to myocardial damage, leading to heart block).
- AV block related to inferior MI is usually transient, with a narrow QRS escape rhythm. In contrast, AV block related to anterior MI is usually below the AV node and can lead to a wide QRS escape rhythm, which is often unstable, due to associated myocardial damage. Transvenous pacing should be considered in the latter case or in the former case if the patient is unstable. Permanent pacing should be considered if AV block does not resolve by day 5 post-MI.

Complications post-MI: fever and thrombosis

Thrombosis

- LV thrombus develops in individuals who have had an anterior MI.
- This can ↑ the risk of CVA.
- Those with an LV thrombus should be commenced on oral anticoagulants (warfarin), which should be considered up to 6 months, with duration guided by repeat imaging and assessment of bleeding risk.

Fever

- This is often seen and peaks 3–4 days post-MI. It may be associated with elevated white cell count (WCC) and raised CRP.
- Other causes of fever should always be considered (infection, thrombophlebitis, venous thrombosis, drug reaction, pericarditis).

Myocardial infarction with non-obstructed coronary arteries

Epidemiology

- 6% of patients (more commonly women) presenting with acute MI. Individuals are generally younger than those with obstructive CAD.

Aetiology

- Plaque disruption.
- Coronary artery spasm.
- Coronary thromboembolism: hereditary thrombophilia disorders (factor V Leiden, protein S and C deficiency) or conditions predisposing to thromboembolism (AF, vegetations, tumours, shunts).
- Coronary dissection: may be related to fibromuscular dysplasia.
- Takotsubo cardiomyopathy (see ➔ Takotsubo cardiomyopathy: overview, p. 278).
- Myocarditis (see ➔ Myocarditis: overview, p. 284).
- PE (see ➔ Pulmonary embolism, pp. 848–9).

Basic pathology

- Myocardial infarction with non-obstructed coronary arteries (MINOCA) is defined as MI in the absence of obstructed coronary arteries (as defined as stenosis of ≥50%), with no other cause for the observed elevated cardiac biomarkers.

Investigations

The following sections will focus on causes of MINOCA not mentioned elsewhere.

- *Bloods:* WCC/CRP, blood cultures (if fever), D-dimer (if PE suspected), thrombophilia screen (factor V Leiden, protein C, protein S, lupus anticoagulant, anticardiolipin antibodies, international normalized ratio (INR)).
- *ECG:* may demonstrate ST-segment elevation/depression, T wave abnormalities, Q wave, and arrhythmias.
- *Echocardiography:* assessment of ventricular function, potential embolic source (vegetations, thrombus, tumour, atrial shunt).
- *Bubble echocardiography:* assessment of atrial septal defect (ASD)/patent foramen ovale (PFO).
- *MRI:* late gadolinium enhancement (LGE) may provide insights into the mechanism of damage. For example, subendocardial LGE suggests an ischaemic cause, whereas subepicardial/mid-wall LGE is more suggestive of myocarditis/cardiomyopathy.
- *Coronary angiography:* intravascular ultrasound (IVUS)/optical coherence tomography (OCT) may help to diagnose plaque disruption or erosion, dissection, or thrombosis.

Prognosis

- The overall 1-year mortality is around 3.5%.

Management

- *Plaque disruption:* DAPT for at least 1 year, together with statin therapy.
- *Coronary thromboembolism:* as per underlying cause.
- *Coronary dissection:* conservative management, as coronary stenting may propagate the dissection.

Chapter 2

Heart failure

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Background and definitions of heart failure

Epidemiology

- HF affects 1–2% of the overall population.
- Its prevalence rises with age and may be >10% in those over 70 years of age.

Definition

- HF is characterized by typical symptoms and signs.
- It can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with, or eject, blood. As a result, the heart fails to meet the metabolic demands of the body.

Forms of heart failure

Acute vs chronic heart failure

- *Acute HF:* is used to describe a patient with rapid-onset symptoms and signs (see ➲ Management of acute heart failure, pp. 108–11).
- *Chronic HF:* those who have had HF for some time.
- *Stable HF:* a treated patient whose symptoms and signs have remained unchanged for over 1 month.
- Patients with chronic HF may deteriorate and develop decompensated HF.

Systolic vs diastolic heart failure

- Most patients with HF have evidence of both systolic (failure of the ventricle to eject blood) and diastolic (failure of the ventricle to relax and fill with blood) dysfunction.
- HF was historically categorized as either HF with preserved ejection fraction (HFpEF) (see ➲ Heart failure with preserved ejection fraction, pp. 106–7) with LVEF ≥50% or HF with reduced ejection fraction (HFrEF) with LVEF ≤40%.
- Recent guidelines have introduced an additional category known as HF with mildly reduced ejection fraction (HFmrEF). HFmrEF is defined as LVEF of 41–49%.

Right vs left heart failure

- Right and left HF refers to whether the patient has either predominantly systemic venous congestion (swollen ankles, hepatomegaly) or pulmonary venous congestion (pulmonary oedema), respectively. These terms do not necessarily indicate which ventricle is most seriously affected.

High-output vs low-output heart failure

- A variety of high-output states may lead to HF (see Box 2.1).
- In high-output states, oxygen demands of peripheral tissues are only met by an ↑ in CO. If there is underlying heart disease, the heart is unable to augment the CO in the long term and HF results. This is characterized by warm extremities and normal or widened pulse pressure. The arterial–mixed venous oxygen saturation (a marker of the ability of the heart to deliver oxygen to metabolizing tissues) is typically normal or even high.

Box 2.1 Causes of high-output heart failure

- Thyrotoxicosis
- Sepsis
- Anaemia
- Pregnancy
- Beriberi
- Paget’s disease
- Arteriovenous fistula (arteriovenous malformation)

- Low-output states are characterized by cool pale extremities, cyanosis due to systemic vasoconstriction, and low pulse volume. The arterial–mixed venous oxygen saturation is typically abnormally low.

Prognosis

- Over the last 30 years, advances in research have significantly improved outcomes. Data from European studies have shown that 12-month all-cause mortality is ~7% in stable patients, with rates of up to 17% in hospitalized patients. The rates of hospitalization are still high, with 12-month hospitalization rates of 30–40%, placing a significant burden on healthcare systems.
- Deaths are usually attributable to sudden death and worsening HF. All-cause mortality is generally higher in HFrEF compared with HFpEF, and in HFmrEF compared with HFpEF.
- Although many risk stratification models exist, their accuracy with regard to predicting mortality is moderate and even poorer regarding hospitalization. Therefore, prediction of an individual’s risk remains a challenge. In a systematic review of models, the most consistent predictors of death were age, gender, renal function, BP, sodium (Na^+) level, LVEF, B-type natriuretic peptide (BNP) level, New York Heart Association (NYHA) class, diabetes, weight or body mass index (BMI), and exercise capacity.

Pathophysiology of heart failure with reduced ejection fraction

- An initial event causes myocardial damage, resulting in an ↑ in myocardial wall stress.
- This is followed by the activation of multiple neuroendocrine systems, including the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS), and the release of cytokines such as tumour necrosis factor (TNF).
- Neuroendocrine activation is also accompanied by structural and metabolic changes in the peripheral skeletal muscle and by abnormalities in cardiopulmonary reflex function such as the baroreflex and chemoreflex. These produce further wall stress, perpetuating this vicious cycle (see Fig. 2.1).

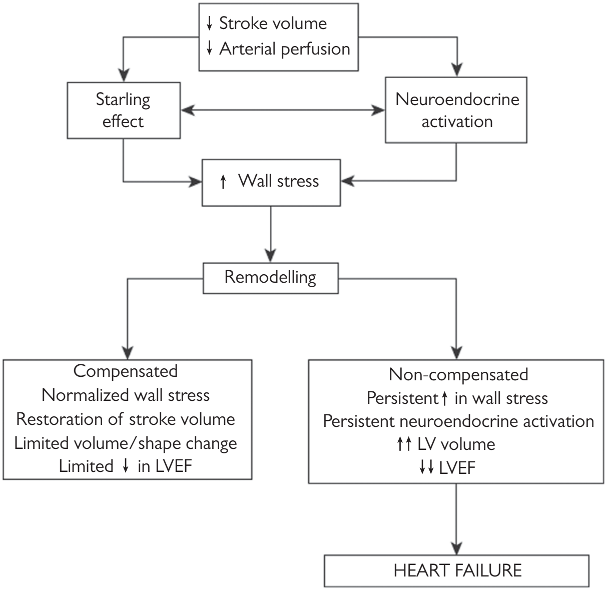
↓ Stroke volume
↓ Arterial perfusion
Starling effect
Neuroendocrine activation
↑ Wall stress
Remodelling
Compensated
Normalized wall stress
Restoration of stroke volume
Limited volume/shape change
Limited ↓ in LVEF
Non-compensated
Persistent ↑ in wall stress
Persistent neuroendocrine activation
↑↑ LV volume
↓↓ LVEF
HEART FAILURE

Fig. 2.1 Pathophysiology of heart failure with reduced ejection fraction.

Causes and precipitants of heart failure

It is important to carefully consider the underlying aetiology, as there may be specific exacerbating factors or other diseases that influence patient management. A non-exhaustive list is given in Table 2.1.

Table 2.1 Causes of heart failure

Cause	Conditions
Idiopathic	Up to 50% may be familial
Ischaemic heart disease	Accounts for ~70% of patients in the developed world
Valvular heart disease	Aortic, mitral, pulmonary, and tricuspid disease. Accounts for 10% of patients with heart failure
Hypertension	Most common contributor worldwide
Genetic	(See ➔ Chapter 5)
Congenital heart disease	Atrial and ventricular septal defects
Myocarditis	
Pericardial pathology	Pericardial effusion, constrictive pericarditis
Arrhythmias	Atrial and ventricular tachyarrhythmias, sinus node dysfunction, and conduction disorders
Infiltrative	Direct infiltration or metastatic spread of malignancy, amyloidosis, sarcoidosis, haemochromatosis, lysosomal storage disorders (Fabry disease), glycogen storage disorder (Pompe disease)
Infection	Bacterial, viral, fungal, parasitic
Metabolic	Thyroid disease, diabetes mellitus, acromegaly, growth hormone deficiency, phaeochromocytoma, Conn's disease, Addison's disease, pregnancy/peripartum
Nutritional	Mineral/vitamin deficiency (e.g. thiamine, selenium, iron, phosphate, calcium), obesity, malnutrition (e.g. anorexia nervosa)
Immune-mediated	Autoimmune (rheumatoid arthritis), systemic lupus erythematosus, connective tissue disorders, giant cell myocarditis, eosinophilic myocarditis
Toxins	Alcohol, cocaine, amphetamines, anabolic steroids, chemotherapeutic agents (e.g. anthracyclines), immunotherapy (e.g. monoclonal antibodies), radiotherapy
High-output states	Severe anaemia, thyrotoxicosis, sepsis, arteriovenous malformation
Volume overload	Renal failure, iatrogenic
Pulmonary pathology	Pulmonary hypertension, pulmonary embolism

Precipitating factors

- A number of studies have demonstrated that a precipitating cause for emergency admissions to hospital with HF can be identified in up to two-thirds of patients.
- *Inappropriate reduction in therapy:* self-discontinuation and iatrogenic withdrawal of diuretics, ACEis, and β-blockers are recognized precipitants.
- *Cardiac arrhythmias:* most commonly AF, but any tachyarrhythmia will further reduce LV filling and stroke volume and may exacerbate ischaemia. Marked bradycardia reduces CO, especially if stroke volume cannot increase any further.
- *Myocardial ischaemia or infarction:* exacerbates LV dysfunction and may worsen MR due to ischaemia of papillary muscles.
- *Infection:* respiratory infections are more common, but any systemic sepsis can precipitate HF due to a combination of factors such as direct myocardial depression from inflammatory cytokines, sinus tachycardia, AF, and fever.
- *Anaemia:* this causes a high-output state that may precipitate acute HF and may exacerbate underlying ischaemia.
- *Concomitant drug therapy:* drugs that directly depress myocardial function (e.g. calcium antagonists—verapamil, diltiazem; many antiarrhythmics; anaesthetics; over-enthusiastic initiation of β-blockers), as well as drugs causing salt and water retention (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oestrogens, steroids, cyclo-oxygenase 2 (COX-2) antagonists), may precipitate HF.
- *Alcohol:* this is directly toxic and, in excess, can depress myocardial function, as well as predispose to arrhythmias.
- *PE:* the risk increases in the immobile patient with low-output state and in AF.
- *Lifestyle/psychological factors:* including depression, as well as poorer compliance with pharmacological management and fluid restriction.

Conditions mimicking heart failure

- Obesity
- Chest disease (lung, diaphragm, chest wall)
- Drug-induced ankle swelling (dihydropyridine calcium channel blockers)
- Drug-induced fluid retention (e.g. secondary to NSAIDs)
- Hypoalbuminaemia
- Renal disease
- Renal artery stenosis
- Hepatic disease
- Severe anaemia
- Thyroid disease

Clinical features of heart failure

The evaluation of a HF patient should start with a comprehensive history and clinical examination. Common symptoms and signs are listed in Table 2.2. Symptoms may be classified according to the NYHA HF classification (see Table 2.3).

Table 2.2 Symptoms and signs of heart failure

Symptoms	Signs
• Shortness of breath • Reduced exercise tolerance • Paroxysmal nocturnal dyspnoea • Orthopnoea • Oedema • Fatigue	• Raised jugular venous pressure • Laterally displaced apex • Third heart sound • Peripheral oedema (sacral, scrotal, ascending oedema from the ankle) • Crepitations and/or reduced air entry at lung bases • Hepatomegaly • Ascites • Cachexia

Table 2.3 NYHA classification of heart failure

Class I	No limitation of physical activity
Class II	Slight limitation of physical activity—symptoms with ordinary levels of exertion (e.g. walking upstairs)
Class III	Marked limitation of physical activity—symptoms with minimal levels of exertion (e.g. dressing)
Class IV	Symptoms at rest

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Non-cardiovascular clinical features

Given that HF can affect multiple systems, it is not unusual for patients to present with:

- *GI symptoms:* secondary to congestive hepatomegaly, ascites, reduced bowel perfusion, and oedema, leading to abdominal distension, pain, anorexia, bloating, nausea, constipation, and jaundice.
- *Genitourinary symptoms:* secondary to impaired renal perfusion, leading to oliguria/anuria, urinary frequency, and/or nocturia.
- *Cerebrovascular symptoms:* secondary to cerebral hypoperfusion and associated electrolyte abnormalities, leading to confusion, memory impairment, anxiety, headaches, insomnia, nightmares, psychosis with disorientation, delirium, and hallucinations.
- *Musculoskeletal symptoms:* gout, carpal tunnel syndrome, muscle cramps.

Diagnosis and investigations for heart failure

Any patient presenting with symptoms and signs for the first time should be evaluated for the probability of HF (see Fig. 2.2).

- In those without a history of precipitating conditions for HF, and with no clinical features of HF and a normal resting ECG, HF is unlikely. Other diagnoses should be considered.
- If history/examination/ECG are abnormal, natriuretic peptides (BNP and N-terminal pro-BNP (NT-proBNP)) should be measured.
- Natriuretic peptides are a useful diagnostic tool to help decide which patients would need to undergo echocardiography.

BNP cut-off values

- *Acute setting:* BNP >100pg/mL and NT-proBNP >300pg/mL.
- *Outpatient setting:* BNP >35pg/mL and NT-proBNP >125pg/mL.
- Due to high negative predictive values and comparatively lower positive predictive values, useful to rule out the diagnosis.
- Levels may be ↑ in elderly patients and those with AF and renal failure. May be ↓ in obese patients.

Investigations for all patients with suspected heart failure

- *ECG:* a normal ECG is unlikely in patients with HF (sensitivity 89%). Common findings are: arrhythmias, conduction defects, voltage criteria for LVH, ST/T wave changes.
- *Blood tests:* FBC, U&Es, LFTs, thyroid function tests (TFTs), iron studies, glucose, HbA1c, lipid profile, uric acid, and BNP (an ABG may be useful in a hypoxic patient in the acute setting).

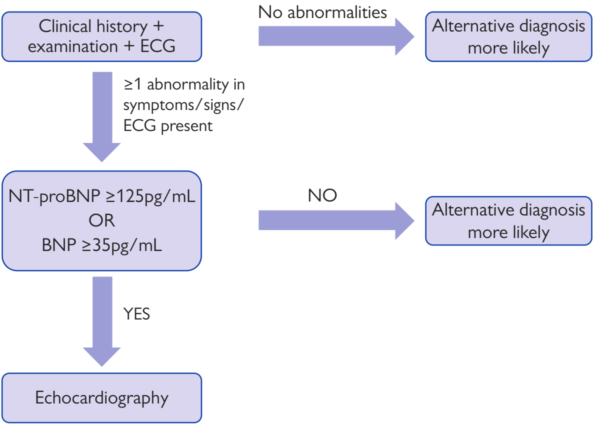
Clinical history + examination + ECG
No abnormalities
Alternative diagnosis more likely
≥1 abnormality in symptoms/signs/ ECG present
NT-proBNP ≥125pg/mL OR BNP ≥35pg/mL
NO
Alternative diagnosis more likely
YES
Echocardiography

Fig. 2.2 Algorithm for the diagnosis of heart failure.

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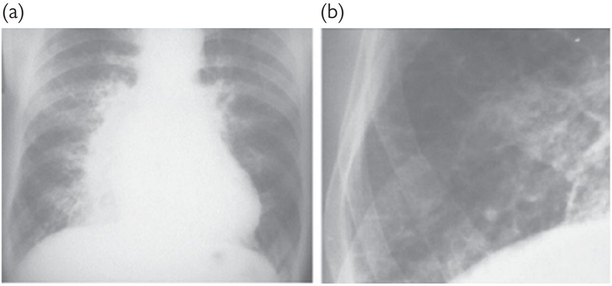

Fig. 2.3 Chest X-ray in heart failure. (a) There is cardiomegaly, prominent upper lobe vessels, and alveolar oedema (bat wing shadowing). (b) Magnified view of Kerley B lines from interstitial oedema.

- *CXR*: permits assessment of pulmonary congestion and non-cardiac causes of dyspnoea. Common findings are: cardiomegaly, pulmonary congestion with alveolar oedema, prominent upper lobe vessels, Kerley B lines, and pleural effusions (see Fig. 2.3).
- *Echocardiography:* the most useful tool in the assessment of HF. Enables assessment of systolic and diastolic LV and RV function (see ➔ TTE: standard measurements, pp. 498–9); may identify causes/complications of HF.

Investigations for selected patients with heart failure

- *Ambulatory ECG monitoring:* for assessment of arrhythmias.
- *TOE:* useful to assess valve disease and identify atrial thrombi in those with AF requiring cardioversion.
- *Stress echocardiography:* used to assess inducible ischaemia. Also useful to assess low-flow, low-gradient AS and dynamic MR.
- *Cardiopulmonary exercise testing (CPET):* used to assess dyspnoea, to guide exercise prescription, and for pre-heart transplant evaluation.
- *Cardiac MRI:* gold standard for assessing ventricular volumes/mass. Can characterize myocardial tissue, fibrosis, and scar. Ischaemia and viability may also be evaluated.
- *SPECT or PET:* options to assess ischaemia/viability; use is limited due to radiation.
- *Coronary computed coronary angiography (CTCA):* used to assess coronary anatomy in those with a low/intermediate pre-test probability of CAD or equivocal stress testing.
- *Coronary angiography:* used to assess coronary anatomy in those with a high pre-test probability of CAD and is recommended in those with aborted cardiac arrest, ventricular arrhythmias (symptomatic), and angina not relieved by medical therapy.
- *Right heart catheterization:* enables evaluation of pulmonary hypertension (PHT) prior to transplantation and further assessment/reversibility of possible PHT identified by echocardiography.
- *Genetic testing* (see ➔ Chapter 5).
- Further testing is governed by the suspected underlying HF aetiology (e.g. pulmonary function testing, endomyocardial biopsy).

Management in chronic heart failure

- The aim of management is to improve symptoms and prognosis; therefore, a great deal of therapy is aimed at modifying risk factors such as control of hypertension and management of diabetes (see ➲ CAD: risk factor modification, pp. 14–15;). Lifestyle modifications, such as reducing alcohol intake and increasing exercise (see ➲ CAD: risk factor modification, pp. 14–15), reduce the risk of developing HF.
- HF management requires a multidisciplinary approach, necessitating the involvement of a number of healthcare professionals in the community, as well as in secondary care. This may include general practitioners (GPs), cardiologists, HF nurses, cardiac rehabilitation teams, dieticians, psychologists, and cardiac surgeons.
- Education of the patient and relatives (see Table 2.4) is essential.
- As a chronic condition, it is essential to monitor progress and response to therapy. This may be achieved by home visits, in the community, or in hospital clinics and through remote monitoring such as structured telephone support.

Table 2.4 Essential topics in patient education with associated skills and appropriate self-care behaviours

Educational topics	Skills and self-care behaviours
Definition and aetiology	Understand the cause of heart failure and why symptoms occur
Symptoms and signs	Monitor and recognize signs and symptoms. Record daily weight, recognize rapid weight gain, and know how and when to notify healthcare provider Use flexible diuretic therapy if appropriate
Pharmacological treatment	Understand indications, dosing, and effects of drugs. Recognize the common side effects of each drug
Risk factor modification	Understand the importance of smoking cessation, BP control if hypertensive, glucose control if diabetic, and weight loss
Diet recommendation	Sodium restriction if prescribed. Fluid restriction of 1.5–2L/day in patients with severe heart failure Increase intake when hot, and during periods of dehydration, including diarrhoea and vomiting
Exercise recommendation	Understand the benefits of exercise and perform exercise training regularly
Sexual activity	Discuss problems with healthcare professionals. Be reassured about engaging in sexual intercourse and understand specific sexual problems and various coping strategies
Immunization	Receive immunization against infections such as influenza and pneumococcal disease
Sleep and breathing disorders	Recognize preventive behaviour such as ↓ weight in obese patients, smoking cessation, abstinence from alcohol
	Learn about treatment options if appropriate
Adherence	Understand the importance of following treatment recommendations
Psychosocial aspects	Understand that depressive symptoms and cognitive dysfunction are common in patients with heart failure, and the importance of social support
Prognosis	Understand important prognostic factors and make realistic decisions Seek psychosocial support if appropriate

Source: data from McDonagh TA, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021:**42**;3599–726.

Pharmacological therapy in chronic heart failure

- Fig. 2.4 illustrates the pharmacological management algorithm in the management of HFrEF. For further information on listed medications, see ➜ Chapter 17. For further information on device implantations, see ➜ Device therapy for heart failure, p. 112.
- Recommended doses are listed in Table 2.5.
- There have been no large randomized controlled trials performed on HFmrEF. However, the ESC guidelines recommend diuretics and consideration of ACEi/ARB/angiotensin receptor–neprilysin inhibitor (ARNI), β-blockers, and MRAs to reduce the risk of hospitalization and death.

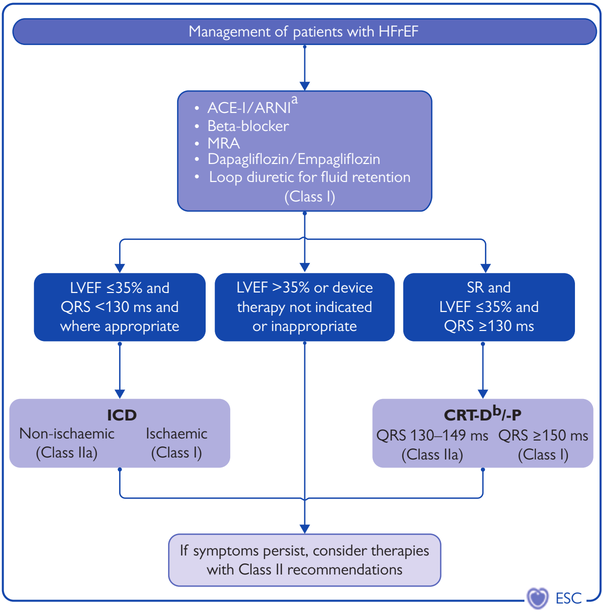
Management of patients with HFrEF
• ACE-I/ARNI[a]
• Beta-blocker
• MRA
• Dapagliflozin/Empagliflozin
• Loop diuretic for fluid retention
(Class I)
LVEF ≤35% and QRS <130 ms and where appropriate
LVEF >35% or device therapy not indicated or inappropriate
SR and LVEF ≤35% and QRS ≥130 ms
ICD
Non-ischaemic (Class IIa)
Ischaemic (Class I)
CRT-D[b]/-P
QRS 130–149 ms (Class IIa)
QRS ≥150 ms (Class I)
If symptoms persist, consider therapies with Class II recommendations
ESC

Fig. 2.4 Pharmacological management of heart failure with reduced ejection fraction. ACE-I, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; SR, sinus rhythm; ICD, implantable cardioverter–defibrillator; CRTD/P, cardiac resynchronization therapy defibrillator/pacemaker. [*] ESC Class II recommendations if symptoms persist: ivabradine, digoxin, hydralazine, and nitrates.

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Table 2.5 Recommended doses of medications in heart failure

Class of drug and examples	Lowest dose	Target dose
Angiotensin-converting enzyme inhibitors		
Ramipril	2.5mg bd	5mg bd
Enalapril	2.5mg bd	10–20mg bd
Lisinopril	2.5–5mg od	20–35mg od
Captopril	6.25mg tds	50mg tds
β-blockers		
Bisoprolol	1.25mg od	10mg od
Carvedilol	3.125mg bd	25mg bd
Metoprolol (CR/XL)	12.5–25mg od	200mg od
Nebivolol	1.25mg od	10mg od
Mineralocorticoid receptor antagonists		
Eplerenone/spironolactone	25mg od	50mg od
Angiotensin receptor blockers		
Candesartan	4–8mg od	32mg od
Losartan	50mg od	150mg od
Valsartan	40mg bd	160mg bd
Angiotensin receptor–neprilysin inhibitor		
Sacubitril/valsartan	24/26mg bd	97/103mg bd
Sodium–glucose cotransporter 2 inhibitor		
Dapagliflozin/empagliflozin	10mg od	10mg od
I_f channel blocker		
Ivabradine	5mg bd	7.5mg bd
Diuretics		
Furosemide	20–40mg od/bd	40–240mg od/bd
Bumetanide	0.5–1mg od/bd	1–5mg od/bd
Thiazides		
Bendroflumethiazide	2.5mg od	2.5–10mg od
Metolazone	2.5mg od	2.5–10mg od
Hydralazine/isosorbide dinitrate	25mg tds/20mg tds	75mg tds/40mg tds
Digoxin	62.5mcg od	250mcg od

bd, twice daily; od, once daily; tds, three times daily.

Adapted from McDonagh TA, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021:**42**;3599–726.

Specific pharmacological therapies in chronic heart failure

Angiotensin-converting enzyme inhibitors

Indications

- ACEis ↓ morbidity/mortality in asymptomatic/symptomatic HFrEF (CONSENSUS, SOLVD-TREATMENT, SAVE, and ATLAS trials).

Contraindications

- ACEis are contraindicated in patients who are pregnant, or who have a history of angio-oedema or known bilateral renal artery stenosis.

Angiotensin receptor blockers

- ARBs have not consistently been shown to ↓ mortality (CHARM/Val-HeFT). Consider in those unable to tolerate ACEis/ARNI.

β-blockers

Indications

- β-blockers ↓ morbidity and mortality in symptomatic HFrEF (e.g. COPERNICUS, CIBIS-II, MERIT-HF, and SENIORS trials).
- β-blockers are also indicated in those with previous MI and asymptomatic LV systolic dysfunction.

Contraindications

- Those with higher-degree heart block (second degree and above) and critical limb ischaemia. Asthma is a relative contraindication.

Practical considerations

- Therapy should be started at a low dose when the patient's HF is stable due to the risk of exacerbating symptoms.

Mineralocorticoid/aldosterone antagonists

Indications

- Studies such as RALES and EMPHASIS-HF showed that in symptomatic patients (already on ACEi and β-blocker) and with LVEF ≤35%, MRAs ↓ mortality and HF hospitalization.

Contraindications

- MRAs are contraindicated in hyperkalaemia and Addison's disease.

Diuretics

Indications

- Diuretics are essential to reducing symptoms and signs of overload.
- Loop diuretics (e.g. furosemide/bumetanide) cause intense diuresis.
- May be combined with thiazide diuretic (e.g. bendroflumethiazide).

Practical considerations

- If there is an insufficient response, consider ↑ diuretic dose, switching from furosemide to bumetanide, or adding an MRA or a thiazide diuretic. Short-term intravenous (IV) therapy may also be an option.
- If ↑ Na^+ concentration and overloaded, then fluid-restrict in the first instance and ↑ diuretic dose. If hypovolaemic, consider ↓/stopping diuretic.

- In ↓ renal function, assess for dehydration, requiring ↓/stopping diuretic; stop other nephrotoxics, and consider ↓ MRA/ACEi/ARB.

I_f channel inhibitor

- Ivabradine inhibits the funny channel (I_f) and ↓ HR. The SHIFT trial showed ↓ mortality and hospitalization in those with symptomatic HFrEF (LVEF ≤35%) and HR of ≥70bpm (SR) who were being treated with a β-blocker, an ACEi, and an MRA. Could also consider in those with contraindications to a β-blocker.

Angiotensin receptor–neprilysin inhibitor

- Sacubitril, a neprilysin inhibitor, is used in combination with valsartan. Inhibiting neprilysin ↓ natriuretic peptide degradation, leading to ↑ cyclic guanosine monophosphate, ↑ diuresis, and myocardial relaxation. Natriuretic peptides also inhibit the RAAS.
- In PARADIGM-HF, patients with HFrEF (≤35%) and ↑ BNP levels were given either an ACEi or an ARNI. ARNIs ↓ hospitalization for HF and mortality when compared to ACEis.
- ARNI commencement should follow a 36h ACEi-free period.

Hydralazine and nitrates

- Limited evidence for a beneficial effect of combined hydralazine and nitrates. In a study of black patients with NYHA class III/IV HF, when hydralazine and nitrates were added to standard therapy, there was ↓ HF admissions and death. Consider in those with symptoms if ACEis/ARNIs are not tolerated or are contraindicated.

Digoxin

- Digoxin may be considered in patients with symptomatic HFrEF in SR, despite treatment with ACEi/ARNI, β-blocker, and MRA, to reduce the risk of hospitalization.

Sodium–glucose cotransporter 2 inhibitors

- SGLT2 inhibitors have shown promise in patients with type II diabetes and HF in ↓ hospitalization. In DAPA-HF, patients with NYHA class II–IV HF and LVEF ≤40% were randomized to the SGLT2 inhibitor dapagliflozin or placebo, in addition to recommended therapy. Risk of death from CV cause or worsening HF was ↓, whether the patient was diabetic or not.
- EMPEROR-REDUCED recruited patients with more severe symptoms and greater LVEF reduction than those in DAPA-HF. Patients were randomized to the SGLT2 inhibitor empagliflozin or placebo, in addition to recommended therapy. The SGLT2 inhibitor ↓ the risk of CVD or hospitalization for worsening HF and ↓ annual estimated glomerular filtration rate (eGFR) decline, regardless of whether the patient was diabetic or not.

Treatments which may cause harm in heart failure

- Glitazones, sulfonylureas, NSAIDs or COX-2 inhibitors, and diltiazem/verapamil may worsen HF.

Heart failure with preserved ejection fraction

Aetiology

- Although causes are similar to those of HFrEF (see ➔ Table 2.1), HFpEF is associated with a high prevalence of hypertension, obesity, diabetes, renal failure, and AF.
- Compared with patients with HFrEF, patients with HFpEF are more commonly older and ♀.

Basic pathology

- HFpEF is defined as LVEF ≥50%.
- It is caused by impaired active ventricular relaxation, as well as by impaired passive ventricular filling, due to ↑ ventricular stiffness.
- The ↑ stiffness leads to ↑ LV end-diastolic pressure and pulmonary venous pressure, which, in turn, leads to ↑ dyspnoea during exercise and even pulmonary oedema.
- Exercise intolerance is thought to be due to a combination of impaired LV filling and inability to utilize the Frank–Starling mechanism, resulting in failure to ↑ CO sufficiently during exertion.

Investigations

- *Bloods:* raised BNP/NT-proBNP (up to 20% have normal levels, particularly if obese).
- *ECG:* this may demonstrate AF and LVH.
- *Echocardiography:* HFpEF patients usually demonstrate ↑ LV mass index (LVMI) (>95g/m^2 (♀), >115g/m^2 (♂)), ↑ relative wall thickness (>0.42), ↑ LA size (>34mL/m^2), ↑ E/e′ >9, and ↑ tricuspid regurgitant (TR) velocity (>2.8m/s).

(See ➔ Diagnosis and investigations for heart failure, pp. 98–9.)

Prognosis

- In patients hospitalized with HFpEF, 50% may be readmitted within a year.
- Mortality is also ↑ after HF hospitalization (up to 4.9% in hospital, 5% within 30 days, and 50% at 5 years).
- Although patients with HFpEF have ↓ rates of all-cause mortality, when compared with those with HFrEF, death is more likely to be due to non-CV causes, compared with worsening HF or sudden death in those with HFrEF.
- Patients with HFpEF also utilize more healthcare resources than those with HFrEF.

Management

- Until recently, there was no convincing therapy shown to reduce mortality and morbidity. However, EMPEROR-PRESERVED showed that empagliflozin was superior to placebo in ↓ CV death or HF hospitalization in symptomatic patients with HFpEF.

- ARNIs may also merit further study. PARAGON-HF assessed the efficacy of ARNIs vs ARBs alone in patients with HFpEF. Sacubitril–valsartan did not lead to ↓ rates of HF hospitalization or death from CV causes. PARALLAX compared an ARNI with optimal background therapy (ACEi/ARB/placebo). Patients treated with an ARNI demonstrated ↓ baseline BNP levels, compared with those on OMT. There was, however, no effect on functional capacity, as assessed by the 6-minute walk test.
- Diuretics are important for symptom control (see ➔ Pharmacological therapy in chronic heart failure, p. 102).
- In those patients in SR, there is some evidence that spironolactone, candesartan, nebivolol, and digoxin may ↓ hospitalization, and in elderly patients, nebivolol may ↓ mortality.
- Managing comorbidities such as hypertension and AF may also improve outcome.

Management of acute heart failure

Definition

- Rapid onset of worsening symptoms and signs of HF.

Clinical features

- Hypoperfusion (peripherally shut down, confusion, oliguria).
- Overload (peripheral oedema, hepatomegaly, ascites, raised JVP, pulmonary congestion).
- May be warm or cold.
- Diagnostic workup of acute HF is shown in Fig. 2.5.
- Other specific evaluation: coronary angiography for suspected ACS and CT pulmonary angiography (CTPA) for suspected PE.

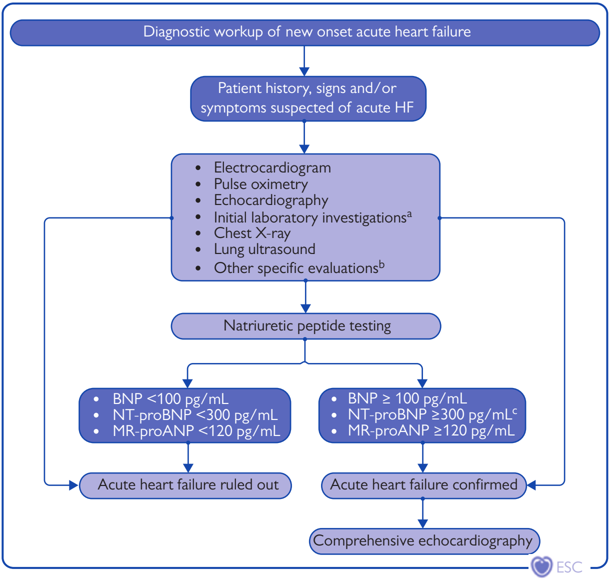
Diagnostic workup of new onset acute heart failure
Patient history, signs and/or symptoms suspected of acute HF
• Electrocardiogram
• Pulse oximetry
• Echocardiography
• Initial laboratory investigations^{a}
• Chest X-ray
• Lung ultrasound
• Other specific evaluations^{b}
Natriuretic peptide testing
• BNP <100 pg/mL
• NT-proBNP <300 pg/mL
• MR-proANP <120 pg/mL
• BNP ≥ 100 pg/mL
• NT-proBNP ≥300 pg/mL^{c}
• MR-proANP ≥120 pg/mL
Acute heart failure ruled out
Acute heart failure confirmed
Comprehensive echocardiography
ESC

Fig. 2.5 Clinical management of patients with acute heart failure. Other specific evaluations include coronary angiography for suspected acute coronary syndrome and computed tomography pulmonary angiography for suspected pulmonary embolism. HF, heart failure; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP; MR-proANP, mid-regional pro-atrial natriuretic peptide.

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Investigations

- *Bloods:* FBC, U&Es, LFTs, TFTs, glucose, NT-proBNP/BNP, troponin, septic screen (CRP and blood cultures) if pyrexial, and D-dimer if PE suspected but may be raised in any case due to HF.
- *ABG:* if hypoxic; otherwise a venous blood gas will suffice in individuals with no indication for ABG to assess pH and lactate.
- *ECG:* may identify ischaemia and arrhythmias.
- *CXR:* is useful to identify non-cardiac causes of deterioration.
- *Echocardiography:* facilitates assessment of structural causes of acute HF.

Management

- Immediate assessment of airway, breathing, and circulation.

Airway management

- Oxygen should only be used in hypoxic patients where oxygen saturation (SpO_2) is <90% or partial pressure of oxygen in arterial blood (PaO_2) is <8kPa, and can be ↑ to a fraction of inspired oxygen (FiO_2) of 100% unless there are other contraindications (e.g. chronic obstructive pulmonary disease (COPD)).
- Non-invasive ventilation (NIV) (CPAP, bilevel positive airway pressure (BiPAP)) should be considered in patients demonstrating signs of respiratory distress such as respiratory rate (RR) >25 breaths/min or SpO_2 <90%). BP may ↓ on NIV initiation.
- Intubation is indicated if PaO_2 is <8kPa, partial pressure of carbon dioxide in arterial blood ($PaCO_2$) >6.65kPa, and pH <7.35 despite NIV.

Initial pharmacological management

- IV diuretics can be given as a bolus dose or as a continuous infusion (20–40mg for those who are diuretic-naïve and at least the equivalent PO dose for those already on diuretic therapy).
- The efficacy of diuresis should be evaluated with a spot urinary Na^+ measurement at 2h. An appropriate diuretic response is defined as a urinary Na^+ level of >50–70mEq/L and/or a urine output of >100–150mL/h at 6h.
- In cases of an inadequate response, the diuretic dose should be doubled. An inadequate response following this may be managed by addition of another diuretic (e.g. metolazone, thiazide).
- If BP is >110mmHg, consider IV vasodilators (e.g. GTN). Patients may develop headache and tolerance with prolonged use.
- Patients in AF and with a ventricular rate of >110bpm should be loaded with digoxin (250–500mcg) PO/IV, with a second dose 6h later, and then a PO maintenance dose of 62.5mcg or 125mcg od. Amiodarone may also be considered.

Inotropes

- Inotropes should be considered if the patient has a BP <90mmHg, with a reduction in CO resulting in organ hypoperfusion (see Table 2.6). First-line inotropic therapy is usually dobutamine.
- Inotropes should be used with caution in patients with tachycardia (>100bpm), as they may exacerbate or precipitate arrhythmias.
- Levosimendan (see Table 2.6) is a unique inotropic agent with dual action: (1) a calcium sensitizer by binding to troponin C in cardiac

myocytes, causing ↑ cardiac contractility and CO; and (2) opening ATP-sensitive potassium channels in vascular smooth muscle, resulting in ↓ systemic and pulmonary vascular resistance. May be used where hypoperfusion is thought to be worsened by β-blockade in order to reverse the effects of the β-blocker. This should be combined with a vasopressor or other inotropes, as it may cause further ↓ BP.

- Type III phosphodiesterase inhibitors, such as milrinone (see Table 2.6), inhibit the breakdown of cyclic adenosine monophosphate (cAMP) and have inotropic and peripheral vasodilating effects, resulting in ↑ CO and ↓ systemic and pulmonary vascular resistance. Their effects are maintained during concomitant β-blocker therapy.
- Vasopressors (e.g. noradrenaline, or dopamine at doses >5mcg/kg/min) should be added to therapy for patients who are still in cardiogenic shock (BP <90mmHg) despite inotropic support (see Table 2.6) to augment BP.

Table 2.6 Emergency drug doses

Drug	Bolus dose	Infusion
Dobutamine (β receptor agonist)	None	2–20mcg/kg/min
Dopamine (β receptor agonist)	None	3–5mcg/kg/min
Levosimendan	Optional 12mcg/kg over 10min	0.1mcg/kg/min, which can be halved or doubled
Milrinone	25–75mcg/kg over 10–20min	0.375–0.75mcg/kg/min
Isosorbide dinitrate	None	1mg/h, increased to 10mg/h
Vasopressors		
Noradrenaline	None	0.2–1mcg/kg/min
Adrenaline	During resuscitation (see ➔ ALS: shockable/non-shockable rhythms, pp. 826–7)	

Ultrafiltration

- Ultrafiltration may be required in patients with potassium levels >6.5mmol/L, pH <7.2, and urea levels >25mmol/L or creatinine levels >300micromol/L.

Mechanical support

- An IABP is only indicated with acute mechanical issues (ventricular rupture, acute MR), severe myocarditis, or peri-procedure in the case of acute myocardial ischaemia.
- Ventricular assist devices (VADs) may act as a bridge to decision-making in some patients.

Admission

- The patient should be admitted onto a medical ward.
- If there is evidence of persistent dyspnoea, tachyarrhythmias, or haemodynamic instability, the patient should ideally be managed in a CCU or HDU.
- Patients requiring intubation and showing severe respiratory distress (e.g. RR >25 breaths/min, SpO_2 <90% despite oxygen therapy), with signs of hypoperfusion, ↓ BP (<90mmHg), bradycardia (<40bpm), or tachycardia (>130bpm), should be managed in intensive care.
- Frequent observations, guided by clinical picture, including HR, RR, BP, urine output (urinary catheterization may be required), and continuous ECG monitoring.
- Disease-modifying therapies should be continued during admission, however only if the patient is haemodynamically stable. Doses may be ↓, or the drug stopped temporarily as required. β-blockers should not be stopped unless there is evidence of cardiogenic shock, given the evidence that stopping β-blockers ↑ mortality in HF.
- Some patients may benefit from therapeutic relief provided by pleurocentesis or abdominal paracentesis.
- Thromboprophylaxis is necessary for any patient not already on anticoagulation where not contraindicated.
- It is important in all patients to correctly identify the precipitating cause (see ➔ Causes and precipitants of heart failure, pp. 94–5) and to instigate appropriate management; for example, there is increasing evidence for revascularization in cardiogenic shock caused by ACS.

Post-acute phase care

- Patient input and output should be recorded carefully on a fluid balance chart.
- Monitoring of daily U&Es and BNP levels.

Criteria for discharge

- Patients should be euvolaemic and on PO therapy (including disease-modifying medication) for 24h.
- Following discharge, review by the HF team at 2 weeks.
- Consider IV iron replacement with ferric carboxymaltose in symptomatic patients with LVEF <45% and iron deficiency (ferritin levels <100ng/mL, or ferritin levels 100–299ng/mL and transferrin saturations <20%).

Device therapy for heart failure

Implantable cardioverter–defibrillator

Ventricular arrhythmias are common in HF, due to both the underlying aetiology and the direct association with ↓ systolic function.

Primary prevention ICD

- An ICD is recommended when a patient is symptomatic (NYHA classes II–III) with LVEF <35% despite ≥3 months of OMT, with ischaemic heart disease (IHD) (ESC Class I recommendation) or a non-ischaemic pathology (ESC Class IIa recommendation), and expected to survive >1 year.
- An ICD should not be considered until 40 days post-MI have elapsed. In these patients, a defibrillator vest may be considered if the risk of arrhythmic events is deemed to be high. This recommendation is based on studies showing there was no benefit seen in patients who had an ICD implanted within a 40-day period post-MI.
- In those patients with QRS ≥150ms, a CRT-D is recommended.
- ICDs are not recommended in those with NYHA class IV HF who are not undergoing consideration for cardiac resynchronization therapy (CRT), VAD, or cardiac transplantation, as they have poor prognosis.
- Subcutaneous devices may be considered for some patients; however, they are limited in their utility regarding bradyarrythmias and cannot provide anti-tachycardia pacing (ATP) or CRT.

Secondary prevention ICD

- ICDs are recommended in patients who have survived a cardiac arrest and those who have symptomatic sustained ventricular arrhythmias, and expected to survive >1 year.

Cardiac resynchronization therapy

- In carefully selected individuals, CRT can improve symptoms and reduce mortality and morbidity (COMPANION, CARE-HF trials). It is recommended in symptomatic patients in SR with QRS ≥150ms (LBBB) (but may also be considered in those with QRS ≥130ms) and LVEF ≤35% despite OMT (ESC Class I recommendation).
- CRT may also be considered in patients with QRS 130–149ms to improve symptoms and reduce morbidity and mortality.
- In those with an ischaemic aetiology, recovery may be impaired by the presence of myocardial scar limiting LV remodelling.
- In patients with HFrEF in any NYHA class and an indication for pacing, CRT is preferable to RV pacing (including in patients with AF), as RV pacing may cause or ↑ interventricular dyssynchrony and exacerbate symptoms.

Advanced heart failure

Definition

Many patients develop advanced HF characterized by symptoms despite maximal therapy. The following criteria are present:

- Severe and persistent symptoms (NYHA classes III/IV)
- Severe cardiac dysfunction (≥1 of: LVEF ≤30%, isolated RV failure, non-operable severe valvular or congenital pathology, persistently raised BNP/NT-proBNP levels, and severe diastolic dysfunction)
- Episodes of congestion requiring IV diuretics or low-output episodes requiring inotropes/vasoactive drugs, or arrhythmias leading to >1 hospitalization in 12 months
- Severe impairment in exercise capacity (6MWT <300m, peak VO_2 <50% predicted).

Management

In patients with advanced HF, short-term mechanical circulatory support (MCS) may be required until long-term MCS or heart transplant becomes available (see Fig. 2.6).

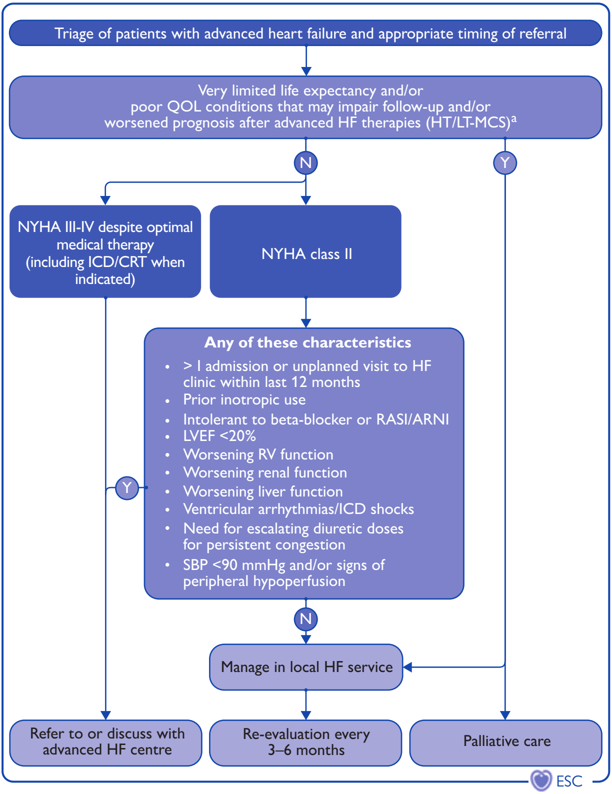
Triage of patients with advanced heart failure and appropriate timing of referral
Very limited life expectancy and/or poor QOL conditions that may impair follow-up and/or worsened prognosis after advanced HF therapies (HT/LT-MCS)[a]
N
Y
NYHA III-IV despite optimal medical therapy (including ICD/CRT when indicated)
NYHA class II
Any of these characteristics
> I admission or unplanned visit to HF clinic within last 12 months
Prior inotropic use
Intolerant to beta-blocker or RASI/ARNI
LVEF <20%
Worsening RV function
Worsening renal function
Worsening liver function
Ventricular arrhythmias/ICD shocks
Need for escalating diuretic doses for persistent congestion
SBP <90 mmHg and/or signs of peripheral hypoperfusion
Y
N
Manage in local HF service
Refer to or discuss with advanced HF centre
Re-evaluation every 3–6 months
Palliative care
ESC

Fig. 2.6 Management of advanced heart failure. QOL, quality of life; HF, heart failure; HT, heart transplantation; LT-MCS, long-term mechanical circulatory support; NYHA, New York Heart Association; ICD, implantable cardioverter–fibrillator; CRT, cardiac resynchronization therapy; RASi, renin–angiotensin system inhibitor; ARNI, angiotensin receptor–neprilysin inhibitor; LVEF, left ventricular ejection fraction; RV, right ventricular; SBP, systolic blood pressure.

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Mechanical circulatory support

Acute heart failure

- MCS may be provided by a percutaneous cardiac support device (IABP) (see ➔ Intra-aortic balloon pump, p. 616).
- Extracorporeal life support (ECLS), including extracorporeal membrane oxygenation (ECMO) (see Fig. 2.7), may assist in those for whom maximal therapy (including inotropes) has been unsuccessful.
- ECMO may serve as a temporary life support measure in those where the pathology is thought to be reversible or as a bridge to other forms of ECLS (e.g. VAD) (see Fig. 2.8).
- The Impella® device is a miniaturized VAD that is inserted percutaneously through the femoral artery.

Extracorporeal membrane oxygenation

Most evidence for ECMO is from case series, cohort studies, and registries. It is important to select the right patients in a timely fashion, as guided by the wider MDT.

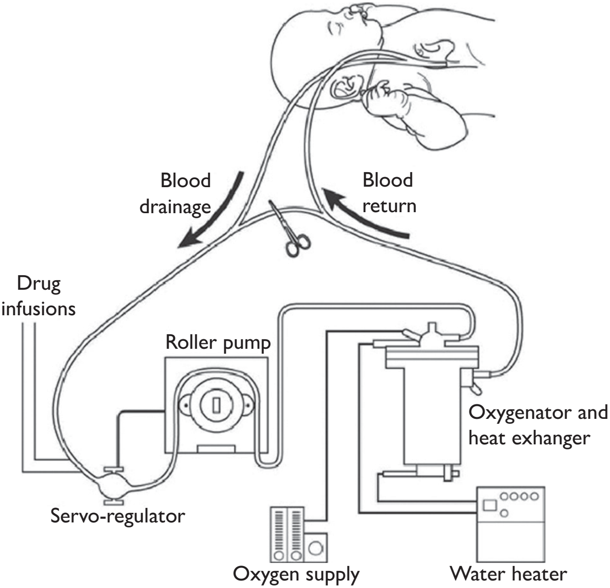
Blood drainage
Blood return
Drug infusions
Roller pump
Oxygenator and heat exhanger
Servo-regulator
Oxygen supply
Water heater

Fig. 2.7 Extracorporeal membrane oxygenation.

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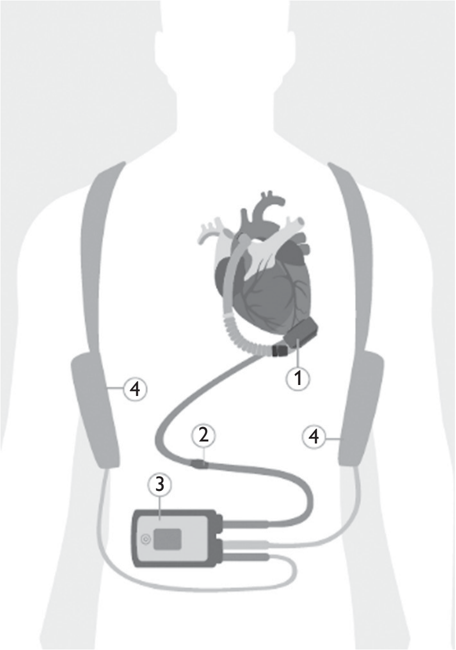

Fig. 2.8 Left ventricular assist device. 1, heart pump; 2, driveline; 3, controller; 4, batteries.
HeartMate3 is a trademark of Abbott or its related companies. Reproduced with permission of Abbott, © 2024. All rights reserved.

Indications

- Post-cardiac arrest.
- Acute MI.
- Fulminant myocarditis.
- Acute HF.
- Peripartum cardiomyopathy.
- Intractable arrhythmias leading to HF.
- Drug toxicity leading to HF.
- Graft failure following transplantation.

Conditions in which ECMO may not be successful

- CVD and/or respiratory disease which is unlikely to recover or lead to transplant.
- Out-of-hospital cardiac arrest (OOHCA) with long periods of low blood flow.
- Severe aortic regurgitation (AR) or type A aortic dissection.
- Refractory septic shock with preserved LV function.
- Severe multiorgan failure.
- Active bleeding.

Mechanism of action

- ECMO passes venous blood through an extracorporeal circuit and returns the blood back to the heart via a semipermeable membrane.
- ECMO can oxygenate the patient and remove carbon dioxide (CO_2), as well as offer haemodynamic support, thermoregulation, and haemofiltration.
- Venovenous (VV) ECMO is used for gas exchange whereby oxygenated blood is returned to a vein. Venoarterial (VA) ECMO is used for cardiorespiratory or cardiac failure. A cannula is inserted into the vena cava or RA (via femoral or internal jugular vein access or centrally). Blood bypasses the lungs and heart, and oxygenated blood returns centrally directly into the ascending aorta or peripherally through the femoral or subclavian artery.

Complications

- Most common is bleeding (e.g. haemorrhagic stroke) due to platelet destruction in the circuit and anticoagulation use due to plastic tubing within the circuit.
- In patients with severe LV dysfunction, ↑ blood flow and pressure created by the circuit can ↑ afterload and worsen LV function.
- Blood may stagnate in the ventricles, leading to thrombus formation.
- Infection can occur at cannulation sites.
- Disruption of distal femoral artery flow may lead to limb ischaemia.

Chronic heart failure

- LVADs were initially used as a short-term bridge to transplantation (BTT).
- Given the shortage of hearts available, LVADs have become a destination therapy in some individuals. In the right patient, survival is comparable to that early after transplantation.
- LVAD therapy may also act as a bridge to candidacy (BTC), enabling recovery of end organ dysfunction and reversibility of contraindications to transplantation (see ➔ Contraindications to heart transplantation, pp. 120–1).
- LVAD therapy may be used to enable ↑ cardiac function where there is a reversible cause (e.g. peripartum cardiomyopathy, myocarditis).
- In a patient with RV dysfunction, a right ventricular assist device RVAD may be considered to assess for reversibility, as RV dysfunction leads to poor outcomes post-transplant.
- In those with biventricular failure, a biventricular assist device (biVAD) should be considered, but unlike an LVAD, outcomes are poor if not used as a BTT.
- Complications of VAD therapy include bleeding, thromboembolism, failure, and infection.
- Artificial hearts function as biventricular, pneumatic, pulsatile pumps, completely replacing the existing ventricles/valves. Artificial hearts should be considered if a VAD is not feasible (e.g. an irreparable VSD or cardiac rupture).

Heart transplantation: indications and workup

- Cardiac transplantation is reserved for those with end-stage HF and severe symptoms, and where no alternative options exist.
- It is a major undertaking for the patient, who must be willing to undergo intensive treatment and be emotionally capable of withstanding the uncertainties that occur both before and after transplantation. The patient must also adhere carefully to immunotherapeutic regimens in order to mitigate the risk of transplant rejection.
- There are significantly fewer donors than potential recipients.

Epidemiology

- Worldwide, 5000 heart transplants are performed annually.

Prognosis

- The 1-year survival presently stands at 85–90%, with median survival of around 12 years.

Indications for heart transplantation

- Patients should not have a contraindication to heart transplantation.

Patients with chronic heart failure

- See ➔ Advanced heart failure, p. 114.

Urgent inpatient referral

- Those who cannot be weaned from inotropic therapy.
- If requiring MCS for cardiogenic shock.
- Those requiring positive airway pressure (PAP) for pulmonary oedema.
- Those with refractory ventricular arrhythmias.

Contraindications to heart transplantation

- Active infection.
- Persistent alcohol/drug abuse.
- Cancer is a relative, not an absolute, contraindication. Should be discussed with an oncologist regarding the likelihood of recurrence.
- Systemic disease with multiorgan involvement.
- Severe cerebrovascular, peripheral arterial, or lung disease.
- Irreversible PHT (PAP >60mmHg, transpulmonary gradient (TPG) ≥15mmHg, and/or pulmonary vascular resistance >5 Wood units). Absolute contraindication if irreversible with pharmacological manipulation or mechanical LV unloading.
- Recent PE (preceding 3 months).
- Irreversible renal dysfunction (eGFR <30mL/min/1.73m^2).
- Serious comorbidities, with poor prognosis.
- BMI ≥35kg/m^2.
- Unlikely to comply with medication due to lack of social support.
- Age is no longer a contraindication; however, patients aged >60 years require careful selection to ↑ likelihood of successful transplant.
- Chronic infection is not an absolute contraindication; individuals with human immunodeficiency virus (HIV) and tuberculosis (TB) may be considered, depending on management.

- LVAD may be useful to assess the reversibility of certain contraindications (e.g. ↑ BMI, renal failure, PHT).
- All cases should be discussed by a cardiac transplant centre MDT.

Investigations for heart transplant workup

- *Anthropometric measurements:* height, weight, BMI.
- *HF prognostic scores:* the Seattle Heart Failure Model* may be used to estimate 1-year survival (if <80%, heart transplantation should be considered).
- *Bloods:* FBC, clotting, U&Es, LFTs, TFTs, iron, HbA1c, NT-pro BNP, bone profile, lipid, sickle cell screen (performed as appropriate).
- *Urine:* microscopy culture and sensitivity, toxicology, albumin:creatinine ratio.
- *Microbiology:* hepatitis A, B, and C, HIV, Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV), *Toxoplasma*, meticillin-resistant *Staphylococcus aureus* (MRSA) screening.
- *Blood group and tissue typing:* allosensitization secondary to pregnancy, previous blood transfusions, or previous transplant may impact how successful a transplant may be.
- *Imaging:* echocardiography, CXR. CT chest/abdomen/pelvis, vascular assessment, renal US, coronary angiography, and/or cardiac MRI (all performed as appropriate).
- *Device therapy:* permanent pacemaker (PPM), ICD.
- *Exercise testing:* CPET (peak VO_2 of <10mL/kg/min is a marker of poor prognosis; in younger patients, a VO_2 of 50% of predicted may be a useful guide of transplant candidacy), 6MWT.
- *Lung function testing.*
- *Right heart catheterization:* mandatory, to assess resistance in pulmonary and systemic vascular beds. Enables measurement of PCWP, PAP, TPG, mixed venous oxygen saturation, and CO.
- *Cancer screening* (if required).
- *Neuropsychological assessment:* may identify mental disorders, coping style, support structure, and understanding of procedure and sequelae. Important for long-term success of the transplant.

* The Seattle Heart Failure Model predicts survival based on baseline demographic features, prior disease, functional status, medications, and results from imaging and laboratory investigations. This model has been prospectively validated in five cohorts including 9942 heart failure patients and 17,307 person-years of follow-up.

Source: data from Bhagra SK *et al*. *Heart*. 2019;**105**:252–60.

Heart transplantation: post-operative considerations

Immunosuppression

- Immunosuppressive therapy begins at the time of transplantation, is ↓ after 3 months, and must be taken lifelong.
- *Induction therapy:* given perioperatively and early post-transplant. This includes polyclonal therapy (antithymocyte globulin) and monoclonal therapy (basiliximab (anti-CD25), alemtuzumab (anti-CD52)).
- *Chronic therapy:* most are started on a calcineurin inhibitor (CNI) such as tacrolimus and ciclosporin, an antimetabolite (mycophenolate mofetil or azathioprine), and a corticosteroid (methylprednisolone, prednisolone). The latter is usually weaned off in most patients.

Complications

- *Graft dysfunction:* this is early failure of graft function (<24h) where there is no evidence of hyperacute rejection, surgical complications, or PHT.
- *Rejection:* this is caused by a reaction between the immune system of the recipient and the donor heart. This may be cell- or antibody-mediated and may be mild to severe. Cell-mediated rejection is common after 1 year. This may be managed by using high-dose corticosteroid therapy for a few days. Antibody-mediated rejection is thought to be due to pre-existing or *de novo* anti-human leucocyte antigen (HLA) antibodies. This can occur acute or late. Antibody removal is performed by using plasma exchange, IV immunoglobulins, or monoclonal antibodies such as rituximab. In general, endomyocardial biopsies are performed frequently in the first year to look for rejection.
- *Infection:* the risk is ↑ by use of immunosuppressive therapy in the first year, and rates of infection improve as immunosuppression therapy is tapered. In the first year, prophylaxis is employed to ↓ risk.
- *Cardiac allograft vasculopathy* occurs where the epicardial arteries are narrowed or become obstructed. The pathophysiology at present is not fully understood but is caused by thickening of the intima due to inflammatory cells, lipid deposition, and smooth muscle cell proliferation). It is thought that some factors increase the risk.

Infection prophylaxis in heart transplantation patients

- *Pneumocystis jirovecii:* co-trimoxazole, pentamidine, or dapsone.
- *CMV:* ganciclovir or valganciclovir.
- *Candidiasis:* fluconazole.
- *Herpesviruses:* aciclovir.
- Patients are advised to undergo immunization against influenza and pneumococcus.
- Live virus vaccines are generally not recommended.

Risk factors for cardiac allograft vasculopathy

- Increasing numbers of acute rejection.
- HLA-DR isotope mismatch.
- Anti-HLA antibodies against donor in recipient.
- Age and gender of recipient.
- Age of donor.
- CAD causing transplantation.
- CMV infection.
- Risk factors for CVD: smoking, hypertension, hypercholesterolaemia.
- Obesity.

- Patients often present with symptoms of HF, and although there is denervation, they may also experience angina. Although this often adopts a diffuse pattern within the arteries, focal lesions may be stented; however, the definitive treatment is repeat transplantation. Statins may delay the onset of this condition.
- *Malignancy:* the risk of malignancy is around 10% up to 5 years after transplant. This is usually caused by viral infections, including EBV, human herpesvirus 8 (HHV8), and human papillomavirus (HPV). The latter virus is the cause for the most common malignancy post-transplant: squamous cell carcinoma of the skin. Sun-damaged skin is a risk factor for multiple and recurrent tumours, and therefore, patients should be advised to protect themselves effectively from the sun. EBV can cause post-transplant lymphoproliferative disease (PTLD), which is a non-Hodgkin's B-cell tumour. HHV8 may also cause Kaposi's sarcoma.
- *Hyperlipidaemia:* this may be caused by the immunosuppressive therapy. Therefore, it is recommended that patients are commenced on a statin post-transplant.
- *Hypertension:* this is more common in ♂ treated with ciclosporin.
- *Renal dysfunction:* this is predominantly precipitated by CNIs and hypertension. In the former case, this is reversible in the acute phase of toxicity, as it is caused by renal arterial vasoconstriction; however, renal dysfunction that occurs later is related to tubular damage and does not reverse, even on cessation of treatment with the CNI.
- *Diabetes:* the risk of diabetes may be ↑ by corticosteroids and CNIs.

Pregnancy

- Pregnancy is generally not advised in the first year.
- The pregnant woman should be managed by an MDT, including the high-risk pregnancy service.
- CNIs and corticosteroids can be continued during pregnancy, with mycophenolate mofetil stopped 6 weeks prior to conception. Men should also discontinue mycophenolate mofetil prior to conception due to potential teratogenicity.
- Levels should be monitored carefully during pregnancy.

Other interventions for heart failure

Valve surgery

- Patients with primary valve disease should be considered for valve repair/replacement surgery (see ➔ Chapter 4).
- Patients with secondary MR benefit from optimization of medical therapy (including CRT). Valvular intervention should be considered for those patients with coronary arteries suitable for revascularization, with evidence of viability and LVEF <30% (see ➔ Mitral regurgitation: management, pp. 204–5).
- MV surgery in patients with severe functional MR and LVEF <30% who cannot be revascularized is questionable but may be considered. Percutaneous MV interventions (e.g. MitraClip) may have a role.
- Surgery for isolated functional tricuspid regurgitation (TR) is not recommended.

Revascularization

- The recent REVIVED trial assessed whether PCI was superior to OMT in patients with LVEF ≤35% and extensive CAD (amenable to PCI), with myocardial viability.
- PCI did not result in a lower incidence of all-cause death or HF hospitalization and calls into question the benefit of revascularization in these patients.

Management of comorbidities in heart failure

Hypertension

Should be treated aggressively in all HF patients (see ➲ Hypertension: investigations, p. 34; ➲ Hypertension: management, pp. 36–9).

Diabetes mellitus

- Tight glycaemic control is recommended, and patients should be treated as per current guidelines.
- *Metformin:* safe in HF but contraindicated in those with renal and hepatic impairment due to the risk of lactic acidosis.
- *Glitazones and sulfonylureas:* associated with ↑ fluid overload and symptomatic HF, and should be avoided if possible.
- *SGLT2 inhibitors (e.g. empagliflozin):* have been shown to reduce HF hospitalizations and mortality.

Hypercholesterolaemia

- If a patient is already taking a statin for known CAD, this should be continued.

Chronic obstructive pulmonary disease

- It may be difficult to diagnose COPD in HF. Therefore, spirometry should be performed once euvolaemic for ≥3 months.
- The majority of COPD patients will tolerate β-blockers well. Cardioselective β-blockers include bisoprolol, metoprolol, and nebivolol.

Iron deficiency anaemia

- Anaemia of chronic disease is common, and it is recommended that patients are periodically screened. IV iron therapy in iron-deficient patients reduces hospitalization and improves symptoms.

Gout

- Gout is common in HF due to high rates of renal dysfunction and concomitant use of loop diuretics.
- Avoid NSAIDs and steroids. Treat acute attacks with colchicine.
- Allopurinol prophylaxis is recommended to prevent recurrence.

Obesity

- In very obese patients (BMI >35kg/m^2), weight loss may improve symptoms and exercise capacity.
- Assess for obstructive sleep apnoea. Manage with specialist input.

Cachexia

- This is defined as involuntary weight loss amounting to ≥6% of body weight in the preceding 6 months to 1 year. Muscle wasting (sarcopenia) also occurs.
- This is managed with appetite stimulants, exercise, anabolic therapies such as testosterone, and supplements.

Palliative care for heart failure

- Patients with clinical features of advanced HF who experience refractory symptoms despite optimal treatment should be referred for a structured palliative care assessment.
- Patients in whom palliative care should be considered include the following:
  - Those with severe functional decline
  - Those with poor quality of life despite optimization of therapy
  - Those not for VAD/heart transplantation
  - Those with frequent admissions despite optimization of therapy
  - Those deemed to be close to the end of life.
- The decision to palliate should closely involve the patient and their family.
- Measures may then be taken to optimize symptom control.
  - Oxygen may provide relief from breathlessness.
  - Opioids may reduce breathlessness and anxiety.
  - Diuretics can be used to alleviate congestion.
  - Medications can be reduced, so that the BP is not precipitously reduced.
  - Stopping medications that do not affect symptom management.
- Decisions regarding resuscitation orders and deactivation of ICDs should be discussed and clearly documented.
- The patient should be consulted on their preferred place of care and death.
- Psychological and spiritual needs of the patient and their family should be discussed.

Further reading

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Ponikowski P, Voors AA, Anker SD, *et al*.; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;**37**:2129–200.

Chapter 3

Arrhythmias

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The cardiac conduction system

Cardiac action potential

The resting cardiac myocyte is electrically negative, with a transmembrane voltage of between −50mV and −95mV. This is due to the distribution of K^+, Na^+, chloride (Cl^-), and calcium (Ca^{2+}) ions across the cell membrane. The negativity is maintained by the energy-consuming Na^+/K^+ pump, which transports three Na^+ ions out of the cell for two K^+ ions inward. During phase 4 of the action potential, the voltage slowly increases until a threshold of around −60mV, at which point voltage-gated Na^+ channels open and trigger depolarization. The voltage changes spread to adjacent cells via gap junctions, such that a wavefront of electrical activation is propagated (see Figs 3.1 and 3.2).

Automaticity

This is the ability of cardiac cells to spontaneously depolarize. It is caused by the inward flow of positive ions while depolarized. At potentials more negative than −60mV, ion channels open, allowing a slow influx of cations. The slow influx of Na^+ and K^+ ions in the sinoatrial node (SAN) allows it to depolarize more rapidly and therefore to suppress other potential pacemaker sites.

Sinoatrial node

The SAN sits high in the lateral RA just below the superior vena cava (SVC). It is 1–2cm long, 2–3mm wide, and <1mm from the epicardial surface. It is the dominant site of impulse generation; impulses are conducted out of the SAN to depolarize the surrounding RA and LA via specialized interatrial connections. The SAN is richly innervated with both adrenergic and cholinergic receptors, which alter the rate of depolarization.

Atrioventricular node

The atrioventricular node (AVN) is located in the RA, anterior to the mouth of the coronary sinus and above the insertion of the septal leaflet of the tricuspid valve. It is the only electrical connection to the ventricle in a normal heart, and like the SAN, it is also densely innervated with sympathetic and parasympathetic fibres.

His–Purkinje system

The electrical impulse conducts rapidly from the AVN through the bundle of His into the upper part of the interventricular septum where it splits into two branches:

- *The right bundle branch:* which continues down the right side of the septum to the apex of the RV and the base of the anterior papillary muscle.
- *The left bundle branch:* which further splits into two fascicles—anterior and posterior. These fascicles travel down the septum and into the LV.

The terminal Purkinje fibres connect with the ends of the bundle branches, forming an interweaving network on the endocardial surface, so that a cardiac impulse is transmitted almost simultaneously to the entire RV and LV.

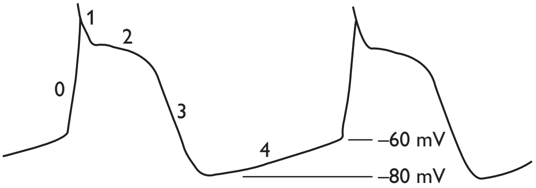

Fig. 3.1 The cardiac action potential.

The ventricular action potential has five parts:

0 rapid influx of Na^+ causing fast depolarization

1 rapid early repolarization due to efflux of Na^+

2 plateau phase where repolarization is slowed by an influx of Ca^{2+}

3 repolarization due to efflux of K^+

4 diastole with a steady-state resting transmembrane voltage.

The plateau phase distinguishes the cardiac from neuronal action potential. The release of Ca^{2+} during phase 2 triggers mechanical contraction of the cell.

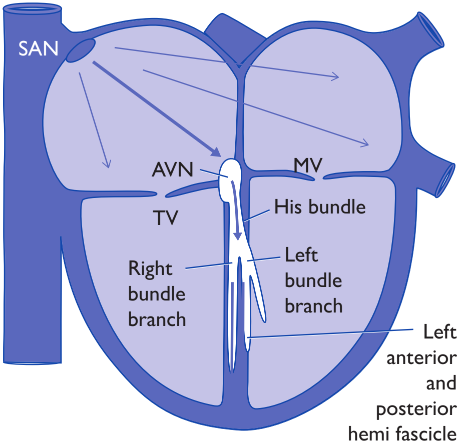
SAN
AVN
MV
His bundle
TV
Left bundle branch
Right bundle branch
Left anterior and posterior hemi fascicle

Fig. 3.2 Anatomy of the normal conduction system. AVN, atrioventricular node; MV, mitral valve; SAN, sinoatrial node; TV, tricuspid valve.

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Arrhythmias: general approach

Arrhythmia presentations are very varied and may involve significant symptoms and haemodynamic compromise. The approach to patients depends on the effect of the rhythm on the patient and the specific arrhythmia.

Effect of the rhythm on the patient

- *Patients with cardiac arrest:* follow ALS guidelines (see ➔ ALS: shockable/non-shockable rhythms, pp. 826–7).[1]
- *Patients with haemodynamic compromise:* patients should have an ECG recorded (important for later diagnosis) and receive emergent management:
  - *Tachycardia:* immediate synchronized DCCV.
  - *Bradycardia:* give atropine 500mcg IV and prepare for transcutaneous pacing.
- *Patients without haemodynamic compromise:* (see Box 3.1) record an ECG and diagnose the arrhythmia before treating according to the diagnosis.

Box 3.1 Features suggesting haemodynamic compromise

- *Shock:* low blood pressure, cool peripheries, sweating
- *Cerebral hypoperfusion:* confusion, syncope, agitation
- *Myocardial ischaemia:* chest pain, diaphoresis
- *Heart failure:* breathlessness, pulmonary oedema

History and examination

- Ask specifically about previous cardiac disease, palpitations, blackouts, dizziness, chest pain, symptoms of HF (CCF), and current medications.
- Ask specifically about conditions known to be associated with certain cardiac arrhythmias (e.g. AF—alcohol, thyrotoxicosis, mitral valve disease, IHD, pericarditis; VT—previous MI, LV aneurysm; complete heart block (CHB)—previous MI).
- Examine carefully, noting the BP, JVP waveform (? cannon waves), heart sounds and murmurs, and signs of CCF.

Diagnosing the arrhythmia

The main distinctions to be made are:

- Tachycardia (>100bpm) or bradycardia (<60bpm)
- Narrow (≤120ms) or broad (>120ms) QRS complex
- Regular or irregular.

Investigations

Table 3.1 lists the investigations for patients with acute arrhythmias.

Table 3.1 Investigations for patients with acute arrhythmias

	Bradycardia	Tachycardia
12-lead ECG and rhythm strip	• Relationship between P waves and QRS complex • A long rhythm strip is sometimes necessary to detect complete heart block if atrial and ventricular rates are similar	• Regular vs irregular rhythm • Narrow vs broad QRS complexes
Blood tests	• Full blood count, biochemistry, glucose (urgently) • Calcium, magnesium (especially if on diuretics) • Biochemical markers of cardiac injury	
Where appropriate	• Blood cultures, C-reactive protein, erythrocyte sedimentation rate; if infection is suspected • Thyroid function tests • Drug levels (e.g. digoxin) • Arterial blood gases	
Chest X-ray	• Heart size • Evidence of pulmonary oedema • Other, non-cardiac pathology (e.g. consolidation, lung mass)	

Reference

1. Resuscitation Council UK (2021). *Adult advanced life support Guidelines*. https://www.resus.org.uk/library/2021-resuscitation-guidelines/adult-advanced-life-support-guidelines

Bradycardia: emergency management

Haemodynamically unstable patients

(See Fig. 3.3)

- *Severe haemodynamic compromise* needs immediate treatment.
- Give *oxygen* via face mask if the patient is hypoxic on air.
- *Keep nil by mouth (NBM)* until definitive therapy has started, to reduce the risk of aspiration in case of cardiac arrest or when the patient lies supine for temporary wire insertion.
- Secure peripheral venous access.
- Give *atropine* 500mcg IV bolus; repeat if necessary, up to a maximum dose of 3 mg. IV *glucagon* can be considered in β-blocker overdose, but the effect is often minimal.
- If remains unstable, consider *isoprenaline* IV infusion (start at 5mcg/min and titrate to HR) if there is a delay in pacing.
- Insert *temporary pacing wire* (technique described in ➔ Temporary pacing: ventricular, pp. 712–13). If this is not possible immediately, set up an *external pacing system* and transfer to a screening room/catheter lab for transvenous pacing.
- Look for, and treat, *reversible causes* (see Box 3.2).

Box 3.2 Common reversible causes for bradycardia

- Acidosis
- Drugs: β-blockers, verapamil, diltiazem, digoxin
- Infective endocarditis*
- Hyperkalaemia
- Hypothyroidism
- Hypothermia
- Hypoxia
- Myocardial infarction

* Bradycardia/heart block in infective endocarditis may or may not resolve as the clinical picture improves—may take days/weeks.

Haemodynamically stable patients

- Assess for high-risk features of asystolic arrest.
- Admit to the CCU, with ECG monitoring.
- *If high risk of asystole:* (see Box 3.3) consider giving atropine 500mcg IV bolus. Have a defibrillator with transcutaneous pacing ability available in the bay/room (see Box 3.4).
- *If not high risk of asystole:* keep atropine drawn up and ready in case of acute deterioration. Avoid temporary pacing wire unless there is haemodynamic deterioration.

Box 3.3 High-risk features for asystolic arrest

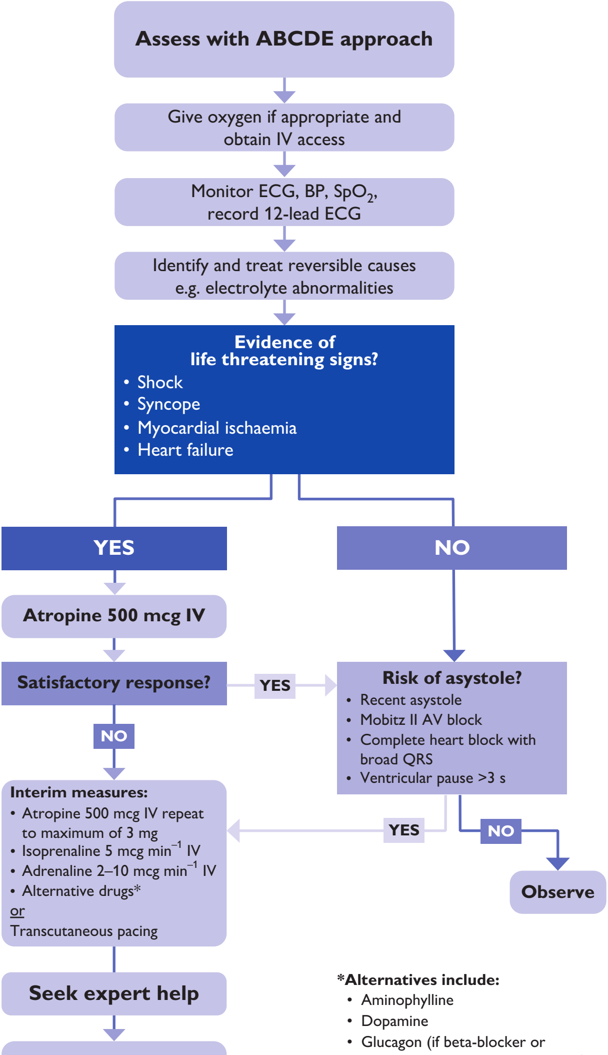
- Recent asystole
- Mobitz type II atrioventricular block
- Complete heart block with broad QRS complex
- Ventricular pause >3s

Long-term management

- Ensure possible *underlying causes* have been identified and removed.
- Regardless of aetiology, if symptomatic bradycardia remains, refer for *permanent pacing* (see ➔ PPM: implantation, pp. 676–7).
- CHB should always be referred for a permanent pacemaker, whether symptomatic or not.

Box 3.4 Transcutaneous cardiac pacing

- In emergencies, transcutaneous cardiac pacing (via an external defibrillator that can pace) may be necessary, but this is only a temporary measure until a more 'definitive' transvenous pacing wire can be inserted.
- The defibrillator pads and ECG electrodes need to be attached.
- Turn the output up (in volts or amperes) until ventricular capture with QRS complexes is seen.
- This will cause extremely unpleasant thoracic muscular capture, so the patient must be sedated (e.g. with a benzodiazepine).
- Haemodynamically stable patients with a high risk of asystole may be managed simply by application of the external pacing electrodes and having the pulse generator ready if necessary.
- Familiarize yourself with the machine in your hospital when you have some time—a cardiac arrest is not the time to read the manual for the apparatus!


Assess with ABCDE approach
Give oxygen if appropriate and obtain IV access
Monitor ECG, BP, SpO_2, record 12-lead ECG
Identify and treat reversible causes e.g. electrolyte abnormalities
Evidence of life threatening signs?
• Shock
• Syncope
• Myocardial ischaemia
• Heart failure
YES
NO
Atropine 500 mcg IV
Satisfactory response?
YES
Risk of asystole?
• Recent asystole
• Mobitz II AV block
• Complete heart block with broad QRS
• Ventricular pause >3 s
NO
Interim measures:
• Atropine 500 mcg IV repeat to maximum of 3 mg
• Isoprenaline 5 mcg min^{-1} IV
• Adrenaline 2–10 mcg min^{-1} IV
• Alternative drugs*
or
Transcutaneous pacing
YES
NO
Observe
Seek expert help
Arrange transvenous pacing

***Alternatives include:**
- Aminophylline
- Dopamine
- Glucagon (if beta-blocker or calcium channel blocker overdose)
- Glycopyrronium bromide can be used instead of atropine

Fig. 3.3 Acute management of bradycardia.

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Sinus node dysfunction

Key facts

- A group of conditions resulting from physiologically inappropriate atrial rates: sinus bradycardia, sinus pauses, sinus arrest, SAN exit block, and inadequate rate response to physiological demands (see Box 3.5).
- Conduction between the atria and the ventricles is normal (unless other pathology is present).

Box 3.5 Causes of sinus node dysfunction

- Ageing: chronic degeneration of sinus or atrioventricular nodes or atria
- Cardiomyopathies
- Drugs: β-blockers, morphine, amiodarone, calcium channel blockers, lithium, propafenone, clonidine
- ↑ vagal tone: vasovagal attack, nausea or vomiting, carotid sinus hypersensitivity
- Jaundice (cholestatic)
- Hypothyroidism
- Hypothermia
- Myocardial infarction or ischaemia of the sinus node
- Myocarditis
- Physiological:* young athletic individual, healthy resting heart, sleep*
- Raised intracranial pressure
- Sarcoidosis

* Sinus bradycardia only.

Sinus bradycardia

- In sinus bradycardia, the SAN discharges <60/min. P waves are normal, but less frequent.
- It may be physiological (e.g. in sleep, healthy resting hearts).
- If symptomatic, reversible causes should be treated. If asymptomatic, no treatment is required.

Sinus pause

- The SAN fails to generate impulses (sinus arrest), or the impulses are not conducted to the atria (SAN exit block).
- A single dropped P wave with a PP interval that is a multiple of the basic PP interval suggests exit block.
- A period of absent P waves suggests sinus arrest.

Sick sinus syndrome

- This syndrome encompasses a number of conduction system problems: persistent sinus bradycardia not caused by drugs, sinus pauses, and paroxysms of atrial arrythmias.
- It is usually diagnosed by ambulatory cardiac monitoring.
- *Tachycardia–bradycardia (tachy–brady) syndrome:* is a variant of sick sinus syndrome where the heart alternates between bradycardia (due to poor sinus node function) and tachycardia (often mediated by AF).

Atrioventricular block

AV block is a group of conditions where electrical impulses are not appropriately transmitted from the atria to the ventricles. This can occur at the AVN (nodal) or His–Purkinje system (infranodal). AV block is further classified as follows.

First-degree atrioventricular block

- Every impulse is conducted to the ventricle, but the conduction time is prolonged. Every P wave is followed by a QRS, but with a prolonged PR interval (>200ms).
- If the QRS width is normal, then the block is more likely to be at the AVN, whereas if the QRS shows aberration (RBBB or LBBB), then the block may be at the AVN or His–Purkinje system.
- Generally benign, but associated with ↑ future risk of AF.

Second-degree atrioventricular block

Impulses are intermittently conducted to the ventricles. There are two distinct subtypes (see Box 3.6):

- *Mobitz type I* (Wenckebach): the PR interval is prolonged until a P wave is not conducted. The PR interval following the dropped P wave must be the shortest. The RR interval is therefore irregular. This block is characteristic of the AVN and is generally considered a benign condition.
- *Mobitz type II:* ECG shows a fixed P-to-QRS ratio of, for example, 2:1, 3:1, or 4:1. The block is predominantly at the His bundle and there is often an aberrant pattern to the QRS complex. May progress to CHB.

Box 3.6 2:1 heart block: Mobitz type I vs type II

- Mobitz type II heart block will commonly result in 2:1 block (two P waves for each QRS complex).
- Severe Mobitz type I (Wenckebach) can also lead to 2:1 block.
- It is not possible to distinguish between these two forms of block in this situation from a single ECG.
- Further ECGs should be obtained to see if different degrees of block occur, which will help separate Mobitz type I from type II.

Third-degree atrioventricular block (complete heart block)

- Impulses are not conducted to the ventricle. The ECG shows dissociation between the P wave and QRS complexes. An escape pacemaker rhythm takes over.
- A narrow QRS indicates AVN block, and the His bundle is the pacemaker, which is faster and more stable than more distal sites.
- A wide QRS indicates infranodal block and a distal ventricular pacemaker site. Asystole may occur; therefore, this carries a worse prognosis.

Treatment

- *First-degree:* no treatment required.
- *Mobitz type I:* generally no treatment required.
- *Mobitz type II:* requires a permanent pacemaker inserted unless an acutely reversible cause is found.
- *Third-degree:* requires a permanent pacemaker inserted unless an acutely reversible cause is found.

Causes

The causes of AV block are outlined in Box 3.7.

Box 3.7 Causes of atrioventricular block

Acutely reversible

- Hypothyroidism
- Hypothermia
- Drugs (β-blockers, digoxin, calcium channel blockers)

Congenital

- Congenital heart block
- Congenital heart disease (atrial septal defect, Ebstein's, patent ductus arteriosus)

Systemic conditions

- Collagen vascular disease (systemic lupus erythematosus, rheumatoid arthritis, scleroderma)
- Granulomatous disease (sarcoid)
- Associated with neuromuscular disease (i.e. myotonic dystrophy)

Cardiac conditions

- Conduction system fibrosis (ageing)
- Associated with acute myocardial infarction or ischaemia
- ↑ vagal tone
- Trauma or following cardiac surgery/catheter ablation
- Calcific aortic stenosis
- Infective endocarditis
- Myocarditis (diphtheria, rheumatic fever, viral, Chagas' disease)
- Cardiomyopathies (haemochromotosis, amyloidosis)

Bundle branch block

This is due to disease in the His–Purkinje system where one of the two conducting bundles fails to transmit signals, leading to slower ventricular depolarization and causing a QRS duration of >120ms.

Left bundle branch block

- *Physiology:* LV depolarization is delayed and the intraventricular septum depolarizes from right to left.
- *ECG findings:* a wide QRS, large notched R waves in leads I and V6, and a deep S wave in lead V1 (see Fig. 3.4).
- *Hemiblock:* block confined to the anterior or posterior fascicles (hemiblock) of the left bundle, giving left or right axis deviation, respectively, on the ECG.
- *Significance:* bundle branch block (BBB) leads to asynchronous contraction of the LV and RV, reducing CO, important in CCF.

Right bundle branch block

- *Physiology:* RV depolarization is delayed and the intraventricular septum depolarizes from left to right.
- *ECG findings:* wide QRS, an RSR pattern in lead V1, and a slurred S wave in leads I and V6 (see Fig. 3.5).
- *Significance:* can be a normal variant, but more commonly as a result of causes listed below and, in addition, ASD, PE, and cor pulmonale.

Bifascicular and trifascicular block

- *Bifascicular block:* RBBB + left anterior hemiblock (left axis deviation on ECG), RBBB + left posterior hemiblock (right axis deviation on ECG). May progress to complete AV block.
- *Trifascicular block:* bifascicular block + first-degree AV block.

Management

- LBBB is normally pathological, and thorough investigation for an underlying cause is needed (e.g. echocardiography, CMR, coronary angiography); however, a cause may not be found.
- RBBB may occur in otherwise completely normal hearts.
- Permanent pacing is not needed for RBBB/LBBB, unless with more advanced block (e.g. symptomatic trifascicular block) or symptomatic bradycardia.

Box 3.8 Common causes of bundle branch block

- Ischaemic heart disease
- Hypertensive heart disease
- Cardiomyopathies
- Conduction system fibrosis (ageing)
- Myocarditis or endocarditis
- Valve disease (e.g. aortic stenosis)
- Pulmonary hypertension
- Trauma or post-cardiac surgery
- Neuromuscular disorders (myotonic dystrophy)

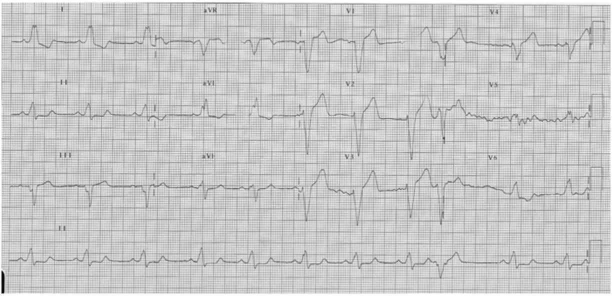
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

Fig. 3.4 ECG showing left bundle branch block. There is a wide QRS complex with large notched R waves in leads I and V6 and a deep S wave in lead V1.

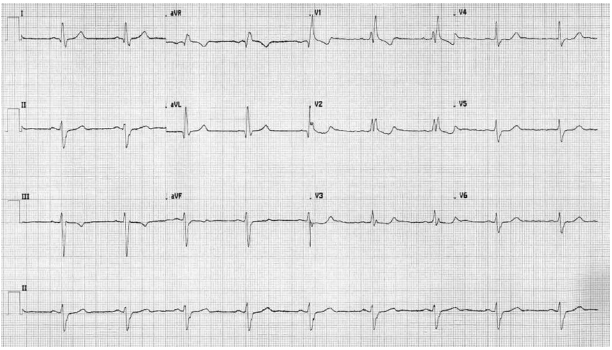
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

Fig. 3.5 ECG showing right bundle branch block. There is a wide QRS complex with an RSR pattern in lead V1 and a slurred S wave in leads I and V6.

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Tachycardia: emergency management

Haemodynamically unstable patients

(See Fig. 3.6)

- Tachyarrhythmias causing severe haemodynamic compromise require urgent correction, usually with external defibrillation. Drug therapy requires time and haemodynamic stability.
- *Oxygen:* give via face mask if the patient is hypoxic
- *Sedate:* if awake, sedate patients with midazolam (2.5–10mg IV) ± diamorphine (2.5–5mg IV + metoclopramide 10mg IV) for analgesia. Beware respiratory depression, and have flumazenil and naloxone to hand.
- *Formal anaesthesia:* general anaesthesia with propofol is preferred, but remember the patient may not have an empty stomach and precautions should be taken to prevent aspiration (e.g. cricoid pressure, endotracheal (ET) intubation).
- *Synchronized shock:* start at 150J and increase as required. Attempt up to three shocks.
- *Arrhythmia unresponsive/recurrent:* correct PaO_2, $PaCO_2$, pH, and K^+.
- *Amiodarone:* if rhythm unresponsive, give amiodarone 300mg bolus IV over 10–20min and repeat synchronized shock.
- *IV Mg^{2+}:* (8mmol stat) may also help to stabilize the myocardium.
- If there is ongoing VT in the context of cardiac arrest or recurrent VT episodes, causing haemodynamic compromise and requiring repeated DCCV, then give IV amiodarone (300mg IV bolus, followed by 900mg IV over 24h via a central venous line). Follow Resuscitation Council UK periarrest arrhythmia guidelines.[1]
- *Exceptions:* in patients with long-standing, persistent AF with an uncontrolled ventricular rate—a synchronized shock is unlikely to cardiovert to SR. Rate control and treatment of precipitant are first line. DCCV should be considered if severely haemodynamically compromised.

Haemodynamically stable patients

- Arrange for continuous ECG monitoring and 12-lead ECG.
- *Assess:* QRS complex broad/narrow, rhythm regular/irregular.
- If the diagnosis is clear, introduce appropriate treatment.
- *If narrow and regular:* likely to be paroxysmal SVT. Try vagal manoeuvres (e.g. Valsalva/carotid sinus massage). If unsuccessful, give adenosine 6mg as a fast IV bolus, followed by 12mg if no response. If required, a subsequent 18mg dose can be given, depending on patient tolerance. Have a continuous ECG rhythm strip running throughout. If adenosine ineffective, then IV β-blockade or verapamil/diltiazem can be considered.
- *If narrow and irregular:* likely to be AF, priority is rate control and treatment of precipitants. Start with a cardioselective β-blocker (e.g. bisoprolol or metoprolol). If features of CCF are present, consider digoxin or amiodarone. Early anticoagulation (LMWH/DOAC) should be considered.
- *If broad and regular:* likely to be VT, unless previously confirmed SVT with BBB. If pulse is present, treat with IV amiodarone 300mg IV over 20–60min and then 900mg over 24h. If no pulse, treat as cardiac arrest.
- *If broad and irregular:* ensure support is present. Possible AF with BBB, pre-excited AF, or polymorphic VT. If unsure, have low threshold for synchronized DCCV. If polymorphic VT, give Mg^{2+}. If drug therapy is

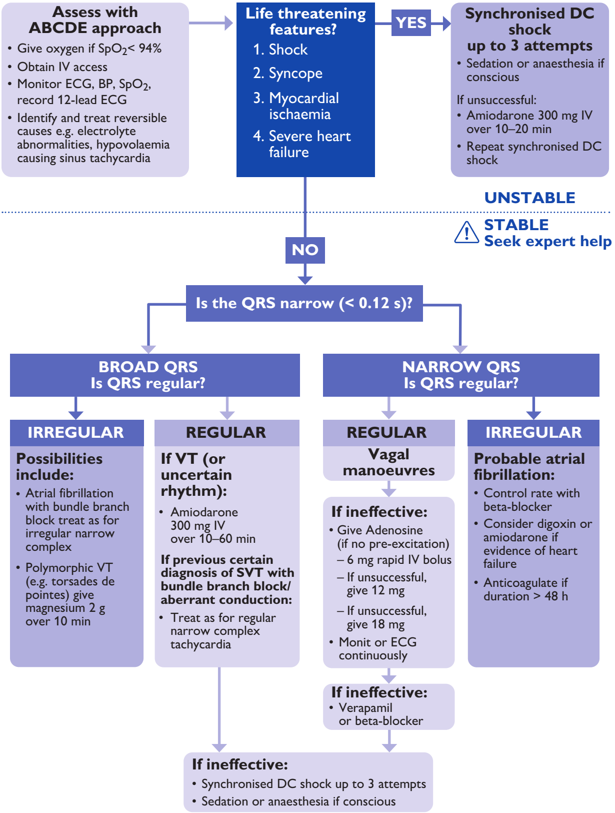
Assess with ABCDE approach
• Give oxygen if SpO2< 94%
• Obtain IV access
• Monitor ECG, BP, SpO2, record 12-lead ECG
• Identify and treat reversible causes e.g. electrolyte abnormalities, hypovolaemia causing sinus tachycardia
Life threatening features?
1. Shock
2. Syncope
3. Myocardial ischaemia
4. Severe heart failure
YES
Synchronised DC shock up to 3 attempts
• Sedation or anaesthesia if conscious
If unsuccessful:
• Amiodarone 300 mg IV over 10–20 min
• Repeat synchronised DC shock
UNSTABLE
STABLE
Seek expert help
NO
Is the QRS narrow (< 0.12 s)?
BROAD QRS
Is QRS regular?
NARROW QRS
Is QRS regular?
IRREGULAR
Possibilities include:
• Atrial fibrillation with bundle branch block treat as for irregular narrow complex
• Polymorphic VT (e.g. torsades de pointes) give magnesium 2 g over 10 min
REGULAR
If VT (or uncertain rhythm):
• Amiodarone 300 mg IV over 10–60 min
If previous certain diagnosis of SVT with bundle branch block/ aberrant conduction:
• Treat as for regular narrow complex tachycardia
REGULAR
Vagal manoeuvres
If ineffective:
• Give Adenosine (if no pre-excitation)
– 6 mg rapid IV bolus
– If unsuccessful, give 12 mg
– If unsuccessful, give 18 mg
• Monit or ECG continuously
If ineffective:
• Verapamil or beta-blocker
IRREGULAR
Probable atrial fibrillation:
• Control rate with beta-blocker
• Consider digoxin or amiodarone if evidence of heart failure
• Anticoagulate if duration > 48 h
If ineffective:
• Synchronised DC shock up to 3 attempts
• Sedation or anaesthesia if conscious

Fig. 3.6 Guidelines to safe management of arrhythmias in the emergency department.
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attempted, ESC guidelines recommend that amiodarone is avoided, procainamide should be considered (ESC Class IIa recommendation), and flecainide can be considered (ESC Class IIb recommendation). However, Resuscitation Council UK still recommends the use of amiodarone at present.

- First episodes of atrioventricular node re-entrant tachycardia (AVNRT) or focal atrial tachycardia (AT) may need no further treatment. All other diagnoses (or if evidence of pre-excitation on a resting ECG) should be referred to a cardiologist for further investigation and management.

Reference

1. Resuscitation Council UK guidelines. Available from: ✎ www.resus.org.uk

Tachyarrhythmias: classification

Fast HRs can be classified in various ways. Below an anatomical approach is used, which can then be subdivided mechanistically. This provides a simple foundation for understanding the ECG appearance and tachycardia mechanism.

Atrial tachyarrhythmias

These are contained completely in the atria (or SAN). Specific subtypes include:

- Sinus tachycardia
- Sinus node re-entrant tachycardia (SNRT)
- AF
- Macro-re-entrant AT (e.g. typical atrial flutter (AFl), atypical RA/LA AFl)
- Focal AT.

Atrioventricular tachyarrhythmias

These are dependent on activation between the atrium and the ventricle (or AVN). They are characterized by:

- AV re-entrant tachycardia (AVRT)
- AVNRT
- Junctional tachycardia.

Ventricular tachyarrhythmias

These are contained completely in the ventricle and include:

- Monomorphic VT
- Polymorphic VT (torsades de pointes (TdP))
- VF.

ECG features of VT are outlined in Box 3.9, whereas SVT causes of broad complex tachycardia are outlined in Box 3.10.

Box 3.9 Features of broad complex tachycardia suggesting a ventricular origin

- AV dissociation—P wave independent of QRS complexes
- Capture and fusion beats
- QRS width >140ms (if right bundle branch appearance) *or* >160ms (if left bundle branch block appearance)
- QRS axis <−30 or >+90
- Concordance of QRS complexes in precordial leads (all positive or all negative)
- Absence of RS or RS interval >100ms in precordial leads

Box 3.10 Supraventricular causes of broad complex tachycardia

- SVT + aberrancy (bundle branch block)
- SVT + pre-excitation (activation of the ventricle over a pathway other than the atrioventricular node)
- Antidromic atrioventricular re-entrant tachycardia
- SVT + class 1c drug (e.g. flecainide)

ECG diagnosis of tachyarrhythmias

- By following simple rules, any tachycardia can be classified into the categories described earlier (see Fig. 3.7); however, the ECG should always be considered in the clinical context.
- A broad complex tachycardia (BCT) should *always* be presumed to be VT in the acute setting, as incorrect treatment may be fatal.
- View the ECG in both tachycardia and the patient's usual rhythm to make a diagnosis (e.g. may see features of pre-excitation).
- For narrow complex tachycardias (NCTs), carotid sinus massage or adenosine boluses can elucidate the underlying atrial rhythm.

1. Is the tachycardia regular?

Grossly irregular RR intervals, regardless of other ECG features, indicate AF. Slight irregularity can occur in other tachycardias, particularly at their onset. Alternatively, atrial and/or ventricular ectopic beats or AT/AFl with variable AV block can give irregularity.

2. Is the QRS complex broad (>120ms)?

A broad QRS complex suggests the heart's conducting system is not being utilized appropriately during ventricular depolarization. If the QRS is broad, a ventricular origin (e.g. VT) should be assumed (see Box 3.11). A narrow QRS complex suggests SVT.

Box 3.11 When can SVT be considered in a broad complex tachycardia?

- If any doubt, always treat BCTs as VT. Treatment for VT will also treat SVT (but SVT treatment will not appropriately manage VT).
- If any history of coronary artery disease, VT is much more likely than SVT.
- SVT should only be considered for a BCT when there is strong clinical suspicion (e.g. young patient, no previous cardiac history, normal ventricular function, no accompanying cardiovascular compromise).
- These patients should be discussed with a senior colleague.
- A sinus rhythm ECG (if available) can be helpful (look for pre-existing bundle branch block or pre-excitation).

3. Identify P waves, their morphology, and P:QRS ratio

- *1:1 P:QRS, normal P wave morphology:* sinus tachycardia, focal AT originating from close to the SAN, or rarely SNRT.
- *1:1 P:QRS, abnormal P wave morphology:* focal AT, AVRT, atypical AVNRT (if slow activation from ventricle to atrium = long RP tachycardia; see Box 3.12), or AFl.
- *P waves not visible:* AVRT or typical AVNRT (with fast activation from ventricle to atrium). Compare QRS morphology in tachycardia with SR, as a slight deflection in the tachycardia QRS complex not seen in SR may represent the P wave.

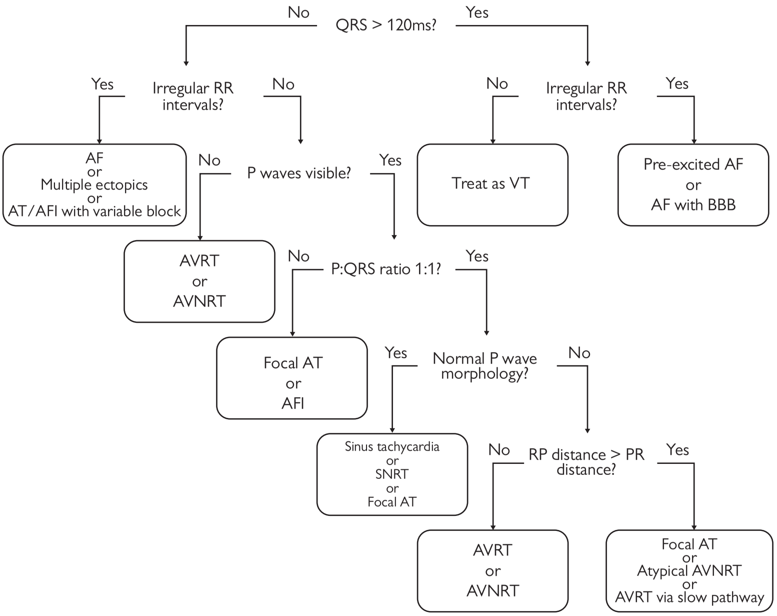
Box 3.12 Long and short RP tachycardia

- *RP interval:* time between the R wave of ventricular depolarization and the P wave (atrial depolarization).
- *Long RP:* a tachycardia is defined as 'long RP' if the RP interval is greater than the PR interval during the arrhythmia. Causes include:
  - Sinus tachycardia
  - AT
  - Atypical (fast–slow) AVNRT
  - SNRT
  - Orthodromic AVRT (slow accessory pathway)
- *Short RP:* where the RP interval is less than the PR interval. Causes include:
  - Typical (slow–fast) AVNRT
  - Orthodromic AVRT (fast accessory pathway)
  - Some ATs

- *P:QRS ratio ≥2:1:* focal AT/AFl with AVN block.
- *P wave rate >250/min:* this defines AFl (macro-re-entrant AT). Usually there will be a 2:1 or 3:1 P:R ratio. In typical AFl, a characteristic sawtooth baseline is seen in the inferior leads.

4. Response to atrioventricular block (adenosine or carotid massage)

- If a rapid P wave rate persists despite induced AVN block, then the tachycardia is independent of the AVN (i.e. macro-re-entrant or focal AT, SNRT, sinus tachycardia).
- If tachycardia is terminated by AVN block, it is either AVRT or AVNRT (rarely junctional tachycardia).
- Focal AT and SNRT may also be terminated by adenosine, not due to AVN block, but because they are adenosine-sensitive.
- Sinus tachycardia may slow transiently in response to adenosine.



QRS > 120ms?
No
Yes
Irregular RR intervals?
Yes
No
Irregular RR intervals?
No
Yes
AF or Multiple ectopics or AT/AFI with variable block
P waves visible?
No
Yes
Treat as VT
Pre-excited AF or AF with BBB
AVRT or AVNRT
P:QRS ratio 1:1?
No
Yes
Focal AT or AFI
Normal P wave morphology?
Yes
No
Sinus tachycardia or SNRT or Focal AT
RP distance > PR distance?
No
Yes
AVRT or AVNRT
Focal AT or Atypical AVNRT or AVRT via slow pathway

Fig. 3.7 ECG diagnosis of tachycardia.

Supraventricular tachycardia

This section deals with the diagnosis and management of individual SVTs (see Fig. 3.8). ➔ Chapter 14 details their mechanisms and ablation.

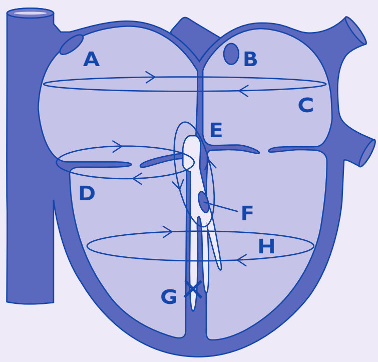


Fig. 3.8 Types of supraventricular tachycardia. A, sinus tachycardia; B, focal atrial tachycardia; C, atrial flutter; D, atrioventricular re-entrant tachycardia; E, atrioventricular nodal re-entrant tachycardia; F, junctional tachycardia; G, bundle branch block; H, ventricular tachycardia.

Sinus tachycardia

Defined as a sinus rhythm (see Box 3.13) with a rate >100/min. May be physiological or pathological; however, pathological causes are extrinsic to the heart itself (see Box 3.14).

Box 3.13 P wave morphology in sinus rhythm

- The sinus node is in the superior and posterior right atrium.
- Atrial depolarization occurs inferiorly and leftward.
- P waves positive in leads II and aVF, and biphasic in lead V1.

Box 3.14 Common causes of sinus tachycardia

Physiological	*Pathological*
• Exercise • Strong emotion • Pregnancy	• Reduced oxygen supply to tissues: anaemia, hypoxia, hypovolaemia, pulmonary embolism • Increased metabolic demand: hyperthyroidism, pain, pyrexia • Drugs (e.g. caffeine, cocaine, salbutamol)

If no underlying cause is found, consider SNRT or focal AT as alternative diagnoses. These will be paroxysmal in nature, have sudden onset or offset, and are usually terminated by IV adenosine. If no underlying cause is found, it may be termed inappropriate sinus tachycardia (see Box 3.15). β-blockers or ivabradine are useful for symptomatic, persistent inappropriate sinus tachycardia (ESC Class IIa recommendation).

Box 3.15 Diagnosis of inappropriate sinus tachycardia

- Exclusion of other SVTs
- Exclusion of other causes (physiological or pathological) or sinus tachycardia
- Normal P wave morphology
- Average heart rate >90bpm, with heart rate >100bpm during waking hours
- May have exaggerated heart rate and blood pressure response to minimal exercise

Sinus nodal re-entrant tachycardia

This is a rare cause of NCT due to a micro-re-entry circuit within the SAN. The ECG is identical to that for sinus tachycardia, as atrial depolarization is coming from the SAN, making diagnosis difficult (requires an electrophysiology (EP) study to confirm).

Treatment options

- β-blockers or CCBs are the first-line treatment.
- Modification of the SAN by radiofrequency ablation (RFA) is reserved for drug-refractory cases or those not wishing to take drugs.

Atrial tachycardia

The term atrial tachycardia describes all regular atrial rhythms arising outside of the SAN with a P rate >100/min, regardless of the mechanism. This should be prefixed by either focal or macro-re-entrant, unless the mechanism is unknown.

Focal atrial tachycardia

- *Pathology:* an automatic atrial focus firing faster than the SAN. Occurs in normal heart but is also associated with cardiac disease.
- *Epidemiology:* generally rare, accounts for 10–15% of patients referred for SVT catheter ablation.
- *Arrhythmia features:* P wave morphology and axis during tachycardia can be used to determine the origin within the atria. Characteristically paroxysmal, with a rate of 150–250/min, but may be incessant.
- *Outcomes:* generally benign, but if incessant, may risk tachycardia-induced cardiomyopathy.
- *Acute treatment:* if necessary, may be terminated with IV adenosine.
- *Long-term treatment:* needed only for symptoms or incessant tachycardia. β-blockers and CCBs can be used to slow the atrial rate and ventricular response by AVN blockade. Class 1c (e.g. flecainide) or class 3 (e.g. amiodarone) may suppress the tachycardia, but use of the latter is limited by toxicity. RFA is the most effective curative therapy.

Macro-re-entrant atrial tachycardia (atrial flutter)

- *Pathology:* caused by a re-entry circuit over large areas of the RA or LA (see ➔ Atrial tachyarrhythmias: mechanism, pp. 654–6).
- *Arrhythmia features:* AFl is an ECG definition; P wave rate >250/min, and no isoelectric baseline between deflections. Not influenced by adenosine; the AVN block reveals the underlying rhythm.
- *Outcomes:* AFl exacerbates CCF symptoms and, if incessant, can worsen LV function. AFl ↑ the risk of developing AF, and patients are thought to have similar risk of stroke.
- *Acute treatment:* DCCV effectively restores SR, but AFl often recurs. Drug therapy has poor efficacy at converting to SR. Rate control through AVN blockade is difficult to achieve; the high doses of β-blockers/CCBs/digoxin required may have side effects.
- *Long-term treatment:* RFA is the most effective way of maintaining SR and is a cure. If curative ablation is not possible, long-term rate control with β-blockers and CCBs may be effective. Class 1c drugs can maintain SR; however, they can accelerate the ventricular rate in AFl by slowing the atrial rate sufficiently to allow the AVN to conduct 1:1. Should always be used in combination with an AVN-blocking agent. Amiodarone is an alternative agent, particularly if LV function is impaired. Ablation of the AVN and a pacemaker are a permanent palliative solution. Anticoagulation recommendations for patients with AFl are identical to those for patients with AF. High-rate atrial pacing can be used in those with an ICD or PPM.

Atrioventricular nodal re-entrant tachycardia

- *Epidemiology*: commonest NCT in those with a normal heart, typically in young adults, women > men.
- *Pathology:* a re-entry circuit is entirely within the AVN (see Figs 3.9 and 3.10).
- *Arrhythmia features*: characteristic paroxysms of palpitations, with pounding in the neck (reflux of blood into the jugular veins caused by simultaneous atrial and ventricular contraction). Benign prognosis and may require no treatment. SR ECG is usually normal.
- *Acute treatment:* usually terminated by IV adenosine or vagal manoeuvres (see Box 3.16). β-blockers or a non-dihydropyridine CCB should be considered if adenosine and vagal manoeuvres fail.
- *Long-term treatment:* can be controlled with β-blockers, verapamil, or diltiazem. Alternative effective, but second-line agents are flecainide, propafenone, and sotalol. The first-line treatment for recurrent symptomatic episodes, however, is RFA, which is a cure. When symptoms are very infrequent, a 'pill-in-the-pocket' approach is sometimes helpful (i.e. a large oral dose of, for example, verapamil is taken to terminate the event).

Box 3.16 Common vagal manoeuvres in supraventricular tachycardia

- *Modified Valsalva manoeuvre:* the patient lies at 45° and blows in a syringe for 15s. Immediately after, they lie flat and their legs are passively raised.
- *Carotid sinus massage:* the carotid sinus is rubbed with moderate digital pressure for 5–10s. Small risk of stroke (<1%). Auscultation for carotid bruits should be undertaken prior to the procedure; if present, carotid sinus massage should NOT be undertaken.

Atrioventricular re-entrant tachycardia

- *Pathology:* this is due to an AV re-entry circuit involving a connection other than the AVN (see Fig. 3.10).
- *Epidemiology:* as accessory pathways are congenital, arrhythmias usually present younger than AVNRT (infancy or childhood). The prognosis may not be benign, and specialist referral is mandatory.
- *Arrhythmia features:* rapid paroxysmal palpitations are the usual symptom. It is usually an NCT (orthodromic), as the ventricle is activated via the AVN; however, a BCT is also possible if the ventricle activates via the accessory pathway (antidromic).
- *Acute treatment:* as with AVNRT (see ➔ Atrioventricular nodal re-entrant tachycardia, p. 151).
- *Long-term treatment:* RFA is the treatment of choice. The most useful drugs are flecainide and propafenone, which slow accessory pathway conduction without slowing the AVN. Verapamil/diltiazem/digoxin should be avoided if ventricular pre-excitation is present.

Junctional tachycardia

This term should only be used for focal tachycardias that originate from the AVN tissue directly and are, in fact, rare in adult cardiology. Distinction from other forms of NCT is only possible from EP studies. RFA is high risk, as the AVN may be damaged. β-blockers and flecainide are effective.

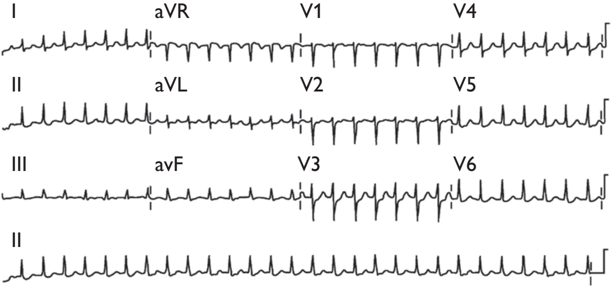


Fig. 3.9 Typical presenting ECG of atrioventricular node re-entrant tachycardia or atrioventricular re-entrant tachycardia. A narrow complex tachycardia without visible P waves.

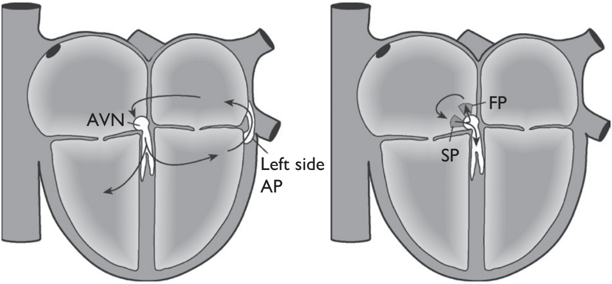


Fig. 3.10 Mechanism of atrioventricular node re-entrant tachycardia (AVNRT) and atrioventricular re-entrant tachycardia (AVRT). Both AVNRT and AVRT have re-entry mechanisms. Orthodromic AVRT via a left-sided accessory pathway (AP) (left). Activation from A to V is down the atrioventricular node (AVN), then across the ventricular myocardium and back from V to A up the AP. The ventricle therefore is an essential part of the circuit. Antidromic AVRT (not shown) would activate in the opposite direction. Typical AVNRT (right) activates from the atrium to the AVN via the slow pathway (SP) and from the AVN to the atrium via the fast pathway (FP), thus completing the circuit. The ventricle is activated as a bystander via the bundle of His and is not an essential part of the circuit. Atypical AVNRT (not shown) activates in the opposite direction.

Atrial fibrillation

Key facts

- AF is the most common sustained cardiac arrhythmia, with a prevalence of 0.5–1% in the general population, but 10-fold higher in those aged over 65 years.
- It is an atrial arrhythmia where uniform activation is replaced by chaotic atrial activation, such that coordinated contractile function is lost and the atria dilate.
- It is characterized by an ECG lacking any consistent P waves, and a rapid, irregularly irregular ventricular rate.

Classification

Many terms are informally used when describing AF. However, an international consensus on nomenclature exists.[1] This allows the correct selection of management options for patients. All episodes of AF lasting >30s should be described as:

- *first detected or a recurrent episode*
- *self-terminating or not self-terminating*
- *symptomatic or asymptomatic*
- *paroxysmal* (if self-terminating within 7 days)
- *persistent* (if cardioverted to SR by any means or lasts >7 days regardless of how it terminates)
- *permanent* (if cardioversion to SR is not possible or is not undertaken)
- *lone* (in the absence of underlying structural heart disease) or *idiopathic* (in the absence of any disease).

Causes

AF is a common end point for many forms of cardiac disease where atrial myocytes are damaged or subject to adverse stress generated by ischaemia, cyanosis, or elevated intracavity or pericardial pressures. These changes alter the conduction properties of the myocardium, facilitating fibrillation (see Table 3.2).

Symptoms and signs

- *Symptoms*: palpitations, dyspnoea, fatigue, presyncope, syncope, and chest pain are common; however, 30% of patients present with AF as an incidental finding only. Ambulatory monitoring reveals that even patients with symptomatic paroxysmal AF have many asymptomatic episodes.
- *Signs*: physical findings are an irregular pulse (which, if rapid, will be faster at the apex than at the wrist), variable intensity of the first heart sound, and absent 'a' waves in the JVP.

Table 3.2 Causes of atrial fibrillation

Common causes	• Hypertension • Left ventricular failure (any cause) • Coronary artery disease • Mitral or tricuspid valve disease • Hypertrophic obstructive cardiomyopathy
Potentially reversible causes	• Obesity • Alcohol binge • Pneumonia • Hyperthyroidism • Acute myocardial infarction • Acute pericarditis • Myocarditis • Exacerbation of pulmonary disease • Pulmonary embolism • Cardiac surgery
Rare causes	• Congenital heart disease • Autonomic 'vagal' overactivity • Pericardial effusion • Cardiac metastases • Myocardial infiltrative diseases (e.g. amyloid) • Atrial myxoma

Reference

1. Levy S, Camm AJ, Saksena S, *et al*. International consensus on nomenclature and classification of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2003;**14**:443–5.

AF: investigations

A reversible cause should be identified early to allow appropriate treatment. The most important investigations are:

- *ECG:* irregularly irregular ventricular rate and absence of P waves. The V rate depends on AVN function. In the presence of complete AVN block, a slow and regular ventricular escape rhythm is present. The QRS will be broad if there is aberrant conduction; ST–T-wave changes may be due to rapid rate, digoxin, or underlying cardiac disease.
- *Echocardiography:* to assess cardiac structure and function—specifically to assess LV function, regional wall motion abnormalities, valve lesions, and pericardial effusion. Enlarged atrial size may provide evidence for longer duration of AF. Atrial size predicts the likelihood of maintaining SR if cardioverted.
- *TOE:* if considering cardioversion to revert the patient to SR, TOE is required to exclude intracardiac thrombus if the patient is not chronically anticoagulated and onset is >48h or unknown.
- *FBC:* anaemia can exacerbate symptoms associated with AF.
- *Thyroid function:* thyrotoxicosis may present as AF only.
- *CXR:* cardiomegaly, pulmonary oedema, intrathoracic precipitant, valve calcification (mitral stenosis (MS)).
- *U&Es:* hypokalaemia as a precipitating cause; renal impairment may impact pharmacological treatment.
- *Troponin or cardiac enzymes:* ? MI. Expect small rise after DC shock. Troponin may be elevated with any prolonged tachycardia without ACS.
- *Drug levels:* especially if taking digoxin.
- *ABGs:* if hypoxic, shocked or ? acidotic.
- *Other investigations:* depend on suspected precipitant.

Other investigations to consider when the patient is stable

Further investigations will be determined by patient characteristics and the results of the above investigations:

- *24h ambulatory monitoring:* may be used to assess HR control and look for episodes of symptomatic bradycardia.
- *Coronary angiography/CTCA:* to examine for IHD in patients with no other risk factors for AF or high-risk features from history/examination/investigations.
- *CMR:* if features suggestive of structural heart disease are identified on echocardiography.

AF: management

Aims of treatment

- The most important aspects of AF management are preventing stroke and controlling the patient's symptoms, *not* restoration of SR.
- Limiting the ventricular rate by pharmacologically blocking the AVN (*rate control*) is safe and often effective.
- Antiarrhythmic drugs (AADs) that maintain SR (*rhythm control*) are limited by their toxicity and efficacy, which explains why a strategy of rhythm control (electrical cardioversion and AADs) may not be better than rate control alone.[1]

Emergency management

- Assess the patient by using a systematic A–E approach.
- If haemodynamically compromised, then urgent external DCCV under general anaesthesia or sedation may be attempted. This is rarely necessary and may not be successful if the patient has long-standing persistent or permanent AF.
- Rate control is usually sufficient to control symptoms and should be attempted first.
- If symptoms persist despite rate control, cardioversion can be attempted pharmacologically (see Box 3.17). Patients must be monitored throughout for possible ventricular arrhythmia and hypotension.
- If AF has been present for >48h, non-emergency cardioversion (electrical or pharmacological) should be preceded by TOE to exclude atrial thrombus (unless already anticoagulated for ≥3 weeks).
- All patients should be anticoagulated for at least 4 weeks post-cardioversion.

Box 3.17 Pharmacological cardioversion of atrial fibrillation

• If no specific concerns about left ventricular function or previous ischaemic heart disease	• Flecainide (2mg/kg, max. 150mg, infused via a peripheral line over 30min)
• If previous ischaemic heart disease or concerned about reduced left ventricular function	• Amiodarone (5mg/kg, max. 300mg infused via a central line)

Rate control

- *When:* generally, rate control should be the first-line strategy in AF management. However, the trials of rate vs rhythm control under-represent younger patients (aged <65 years), so in this group, a strategy of rhythm control may be warranted. Additionally, the EAST-AFNET 4 trial suggests that in those diagnosed ≤1 year prior to treatment, rhythm control may be a superior therapy.[2]

- *Drugs:* the first-line agents are β-blockers or non-dihydropyridine CCBs (verapamil or diltiazem), which are effective during both exercise and rest. Digoxin is effective at rest only and should be considered a second-line agent. Rate control can be assessed by 24h Holter monitoring, ensuring HR at rest is <110 bpm.
- *Pace and ablate:* see below.

Rhythm control

- *When:* if symptoms are not improved by rate control alone, or a reversible cause of AF has been treated, then rhythm control should be attempted.
- *DCCV:* patients should be anticoagulated for at least 3 weeks before and 4 weeks after DCCV. Alternatively, TOE can be undertaken to assess for thrombus in the LA appendage before DCCV. Pads should be positioned in the anterior–posterior position (cf. anterolateral). For persistent AF, SR may be *restored* by DCCV. However, AADs or non-pharmacological methods are usually needed to *maintain* SR and may be started 1–3 weeks before DCCV is attempted.
- *Drugs:* flecainide, propafenone, sotalol, disopyramide, and quinidine are all more effective than placebo in maintaining SR. They all can lead to long QT-related VT/VF and are contraindicated in patients with structural heart disease. Amiodarone is the most effective drug; however, its use is limited by non-cardiac side effects and it is not tolerated by up to 25% of patients. If AVN function and the QT interval are normal, these drugs can safely be started out of hospital. QRS width and QT interval should be monitored on a weekly basis until a maintenance dose is reached.
- *Catheter and surgical ablation:* this is the most effective method of maintaining SR but carries a small procedural risk (see ➔ Catheter ablation of atrial fibrillation, pp. 658–9).
- *Pacemakers:* use of pacemakers to maintain SR has previously been suggested, but evidence supporting this strategy is poor. Pacemakers have the following roles in AF management.
- *SAN disease:* if present, may result in ‘tachy-brady syndrome’ where periods of tachycardia alternate with significant bradycardia, preventing appropriate rate control. Pacemaker implantation prevents bradycardic episodes, allowing for sufficient pharmacological rate control.
- *Pace and ablate:* this is a palliative strategy when symptoms continue because adequate rate or rhythm control is not possible with drugs or by other means such as ablation. A pacemaker is implanted, and 6 weeks following this, iatrogenic CHB is induced with RFA. This can bring dramatic symptom improvement; however, patients are rendered pacing-dependent.

References

1. Wyse DG, Waldo AL, DiMarco JP, et al.; AFFIRM Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;**347**:1825–33.
2. Kirchhof P, Camm AJ, Goette A, *et al*.; EAST-AFNET 4 Trial Investigators. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med*. 2020;**383**:1305–16.

AF: stroke risk and anticoagulation

AF significantly ↑ an individual's risk of stroke. The mechanism of stroke in AF is thought to be via thrombus formation within the LA appendage which can embolize to the brain. The risk of stroke in AF patients is not uniform and can be approximated by using the CHA_2DS_2-VASc score (see Table 3.3).

Table 3.3 CHA_2DS_2-VASc scoring system to assess risk of stroke in atrial fibrillation

Condition	Score
*C*ongestive heart failure	1
*H*ypertension	1
*A*ge >75 years	2
*D*iabetes	1
*S*troke or transient ischaemic attack (TIA)	2
*V*ascular disease	1
*A*ge 65–75 years	1
*S*ex *C*ategory (♀)	1

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When to anticoagulate

- Anticoagulation ↓ the risk of stroke in patients with AF but ↑ the risk of bleeding (intracranial and GI bleeding are of particular concern).
- Decision on whether to use warfarin long term depends on the patient's overall stroke risk, and no distinction should be made between paroxysmal, persistent, or permanent AF.
- Therapeutic anticoagulation is needed for at least 3 weeks pre- (unless TOE is performed) and 4 weeks post-cardioversion.

Anticoagulation should be offered

- *Men:* with CHA_2DS_2-VASc score ≥2.
- *Women:* with CHA_2DS_2-VASc score ≥3.

Anticoagulation should be considered

- *Men:* with CHA_2DS_2-VASc score ≥1.
- *Women:* with CHA_2DS_2-VASc score ≥2.

Falls and anticoagulation

- Falls are associated with ↑ mortality in AF patients.
- There is no evidence that falls markedly ↑ the risk of intracranial haemorrhage.
- Anticoagulation should be continued unless there are severe uncontrolled falls (e.g. epilepsy, advanced multisystem atrophy).

Choice of anticoagulant

Non-vitamin K antagonist oral anticoagulants

- Medications including direct thrombin inhibitors (e.g. dabigatran) and factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban).

- Recommended as first-line anticoagulation in AF by ESC (unless ≥ moderate MS or mechanical heart valve).
- Have a predictable effect and do not require regular monitoring.
- Apixaban 5mg bd ↓ stroke by 21% and major bleeding by 31% c.f. warfarin. Dabigatran 150mg bd ↓ stroke by 35% c.f. warfarin but similar bleeding risk. Edoxaban 60mg od and rivaroxaban 20mg od are non-inferior to warfarin. All DOACs have a degree of renal excretion (apixaban the least (27%)) and dose ↓/avoidance is required. For further details, see ➔ Anticoagulants: factor Xa inhibitors, pp. 754–5.

Warfarin

- With an international normalized ratio (INR) >2 ↓ strokes in AF by 60%, ↓ mortality by 25% compared with control (aspirin/placebo).
- Narrow therapeutic range (requires regular monitoring); can be sub-therapeutic (↓ INR) or cause bleeding complications (↑ INR).
- Time in therapeutic range predicted using SAMe-TT$_2$R$_2$ (see Table 3.4).
- Warfarin should be used (instead of DOACs) in ≥ moderate MS, mechanical heart valves, or significant renal dysfunction. For further details, see ➔ Anticoagulants: vitamin K antagonists, pp. 758–61.

Aspirin or other antiplatelet agents

- ↑ bleeding risk without significant ↓ stroke risk in patients with AF.
- They are not recommended for stroke prophylaxis in AF.
- If patients with AF are on antiplatelet agents for stroke prevention they should be converted to an appropriate anticoagulant.

Left atrial appendage occlusion

- Most strokes in AF are due to thrombus from the LA appendage.
- A device (e.g. Watchman®) is delivered via the femoral vein and a trans-septal puncture to occlude the appendage (see ➔ Left atrial appendage closure, pp. 622–3).
- Demonstrated equivalence to warfarin; however, small procedural risk of stroke and tamponade. Can be considered in patients with high stroke risk and significant anticoagulation contraindications.

Table 3.4 SAMe-TT$_2$R$_2$ score

Condition	Score
*S*ex (♀)	1
*A*ge (<60 years)	1
*M*edical history	1
*T*reatment (rhythm control strategy)	1
*T*obacco use (within 2 years)	1
*R*ace (non-Caucasian)	2

Scores ≤2 suggest the patient is likely to achieve a high time in therapeutic range (e.g. >65%).

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Ventricular tachycardia

This section deals with diagnosis and pharmacological management. Mechanisms and ablation are discussed in detail in ➔ Chapter 14. The most important distinction is the presence of structural heart disease. Impaired LV function is the strongest predictor of a poor prognosis.

Normal heart VT (benign VT)

- VT occurring in a structurally normal heart is generally well tolerated and generally responds to antiarrhythmic medication or RFA.
- Two forms are primarily recognized.

Right ventricular outflow tract tachycardia

- Due to automatic firing cells in the right ventricular outflow tract (RVOT), giving a characteristic ECG pattern of LBBB with a strongly inferior axis (see Fig. 3.11).
- Paroxysms of palpitation are related to exercise or other stressors (due to adrenergic-dependent character of the arrhythmia).
- Usually presents in the second to fourth decade of life.
- Syncope only occurs in around 10% of cases.
- The tachycardia is adenosine-sensitive.
- Symptoms are usually well controlled by verapamil or β-blocker, but RFA is a successful curative option.
- Care must be taken to exclude arrhythmogenic right ventricular cardiomyopathy (ARVC) as the diagnosis, particularly if the ECG or echocardiogram is not typical (see ➔ Arrhythmogenic cardiomyopathy: overview, p. 250).
- Left ventricular outflow tract (LVOT) tachycardia (RBBB + inferior axis) is also recognized.

Fascicular tachycardia

- Its mechanism is uncertain; however, activation emerges from the left posterior fascicle.
- The ECG typically shows RBBB with a superior axis (see Fig. 3.12). It is sensitive to IV verapamil (which normally slows, then terminates it), but not to adenosine.
- Symptoms are well controlled with PO verapamil, but RFA offers a cure.

Minimum investigations

- *ECG:* the resting ECG should be normal. Typical features of ARVC should be excluded (see ➔ Investigations, pp. 252–3).
- *Blood tests:* plasma BNP levels should be normal. Electrolyte disturbance should be ruled out and corrected if necessary.
- *Echocardiography:* transthoracic echocardiography (TTE) should be undertaken to confirm that the heart is structurally normal. If there are any concerns, then cardiac MRI should be undertaken.

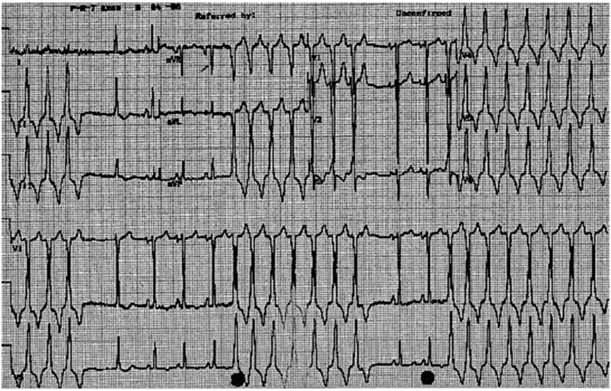
aVR
aVL
aVF
V1
V2
V3
V1

Fig. 3.11 Intermittent RVOT tachycardia and sinus rhythm. During tachycardia beats, notice the LBBB appearance and the positivity in leads II, III, and aVF, indicating an inferior axis.

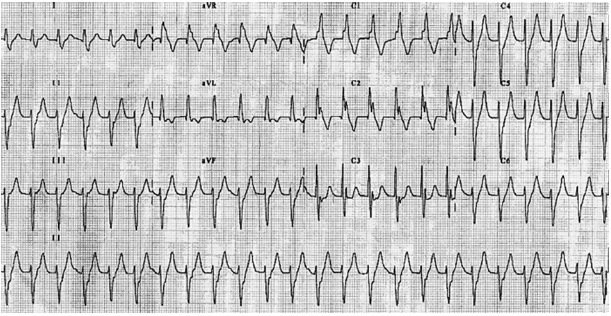
I
aVR
C1
C4
II
aVL
C2
C5
III
aVF
C3
C6
II

Fig. 3.12 A 12-lead ECG of fascicular tachycardia suggested by broad complex tachycardia with an RBBB appearance and a superior axis.

VT with impaired LV function

Symptoms

Palpitations, chest pain, presyncope, syncope, dyspnoea, pulmonary oedema, and sudden death can all occur. How well patients tolerate the arrhythmia depends on their LV function and the tachycardia rate.

Aetiology

- Any cause of impaired LV function can cause VT.
- Common causes are CAD, dilated cardiomyopathy, and hypertrophic obstructive cardiomyopathy (HOCM).
- They are due to re-entry around areas of scarred or diseased myocardium.
- VT may rapidly deteriorate to VF and these patients die suddenly.

General management

- It is essential to treat the underlying CCF (ACEis, β-blockers, diuretics, nitrates, statins).
- Causes for cardiac dysfunction should be sought and treated where appropriate.
- This reduces not only symptoms, but also the incidence of arrhythmia.

Long-term antiarrhythmic treatment

- β-blockers reduce arrhythmia and sudden cardiac death (SCD), but the impact of other drugs is minimal and often harmful.
- Flecainide, propafenone, and sotalol all ↑ mortality in those with impaired LV function and should be avoided, except in patients with an ICD under supervision of an electrophysiologist.
- Amiodarone and mexiletine have a neutral impact on prognosis but may reduce the number of VT episodes in very symptomatic patients. RFA is only possible when VT is haemodynamically well tolerated, therefore limiting its use (see ➔ Ventricular tachycardia: ablation, pp. 672–3).

Preventing sudden cardiac death

- ICDs do not prevent ventricular arrhythmias but have dramatically improved survival for these patients.
- In SCD-HeFT, participants with ↓ LVEF were randomized to ICD, amiodarone, or placebo. Those in the ICD arm had a 23% ↓ mortality, compared with the placebo arm. There was no mortality benefit with amiodarone.
- For specific guidance, see ➔ Indications for implantable cardioverter–defibrillators, p. 685.

Palpitations: general approach

Definition

Palpitations are a patient's awareness of their own heartbeat, whether it is normal, fast, slow, or irregular.

Causes

- See Table 3.5 for common causes.
- Palpitations are generally benign, with most people presenting to a cardiologist having ectopic beats only or no underlying arrhythmia at all.
- Palpitations caused by ventricular arrhythmia or bradycardia are unusual but require urgent investigation and treatment.
- Palpitations are commonly found in patients with anxiety or depression.

Table 3.5 Causes of palpitations

Arrhythmia	Sensing own heart rhythm	Not related to heart

• Atrial or ventricular ectopic beats
• Atrial fibrillation, paroxysmal or persistent
• Other supraventricular tachycardia
• Ventricular tachycardia
• Bradycardia; atrioventricular or sinus node disease
	• Normal
	• Hyperdynamic circulation
	  • Pregnancy
	  • Hyperthyroidism
	  • Anaemia
	  • Fever
	• Physiological tachycardia
	  • Exercise
	  • Anxiety
	  • Caffeine
		• Depression
		• Anxiety

Evaluation

- *Symptom description:* elicit a careful description and ask the patient to tap the rhythm on a desk. Missed beats, sudden thumps, and symptoms lasting for a few seconds suggest atrial or ventricular ectopics; sudden onset/offset of rapid palpitations suggest SVT; irregularity suggests AF.
- *Associated symptoms:* syncope, near syncope, or chest pain suggest a more sinister cause—ventricular arrhythmia or bradycardia.
- *Drug and social history:* carefully review drugs for potential causes. What is the patient's caffeine and alcohol intake?
- *Past medical history:* previous MI, murmurs, or features of CCF suggest an underlying structural heart disease and make ventricular arrhythmia more likely. Consider obtaining an echocardiogram.
- *Investigations:* an abnormal ECG suggests an underlying structural heart disease. Check electrolytes, FBC, and TFTs for underlying causes.

Investigations

All patients require a comprehensive history, physical examination, and 12-lead ECG. Further investigations depend on the patient. Below is a list of potential investigations. Others should be considered if clinically indicated.

• 12-lead ECG	Look for tachycardia/bradycardia Evidence of pre-excitation Evidence of previous MI
• Blood tests	FBC (? anaemia), U&Es, TFTs Ca^{2+}, Mg^{2+} (especially if on diuretics) Biochemical markers of cardiac injury
• Transthoracic echocardiography	Should be considered in patients with a history of heart disease, an abnormal ECG, or frequent/severe palpitations Look for structural heart disease (e.g. old MI, dilated cardiomyopathy, HCM) If normal, then the prognosis is very good, regardless of arrhythmia
• Ambulatory (Holter) monitoring	Continuous recording of patient's cardiac rhythm for 24h, 48h, or 7 days Correlate the symptom diary with the rhythm Ensure an appropriate length of recording (e.g. 24h monitoring is pointless if symptoms occur once a month!)
• Event (loop) recorder	Cardiac monitor that records the heart rhythm on a 5–10min loop Only stores in memory when activated by the patient or if a preset HR is detected (e.g. >160bpm or <40bpm) Can be carried or worn for 2–4 weeks
• Implantable loop recorder	If palpitations are associated with syncope
• Exercise test	If palpitations are precipitated by exertion or associated with chest pain
• EP study	When a definitive diagnosis cannot be made, but tachyarrhythmia is strongly suspected

Management

If an arrhythmia is identified, treat as described previously. In most people, either no abnormality or ectopic beats only will be discovered, and reassurance can be given.

Syncope: general approach

Definition

Syncope is a transient loss of consciousness (blackout) due to a disorder of the circulation. It is a medical emergency, as it may be the first manifestation of an undiagnosed life-threatening condition.

Aetiology

Causes are listed in Table 3.6, and they should be distinguished from the much rarer neurological causes of transient loss of consciousness (e.g. epilepsy).

Table 3.6 Principal causes of transient loss of consciousness

Cardiovascular (=syncope)	*Reflex syncope* (due to neurally mediated reflexes)—has various names: vasovagal ('simple faint'), neurocardiogenic syncope, carotid sinus syncope, situation-related (micturition, cough, swallow), etc.
	Arrhythmia: bradycardia (atrioventricular or sinoatrial nodal disease), ventricular tachycardia, ventricular fibrillation, torsades de pointes (long QT syndrome), Wolff–Parkinson–White syndrome, supraventricular tachycardia (rare)
	Postural hypotension: elderly, antihypertensive or heart failure drugs
	Mechanical problems: severe valvular stenosis, hypertrophic obstructive cardiomyopathy, pulmonary embolism, pulmonary hypertension, aortic dissection
Neurological	Epilepsy, vertebrobasilar ischaemia, migraine
Psychogenic	Factitious, hysteria, panic disorders
Other	Hypoglycaemia, hyperventilation, hypoxia

Evaluation

A systematic approach is required to determine the cause, future risk, and management. A cause will not be found in 10–15% of patients. High-risk patients should not be discharged until a diagnosis is established (see Box. 3.18).

- A clear history is essential, including a reliable witness account if available. Was there truly loss of consciousness?
- *Seizures:* 'aura', tongue biting, tonic–clonic episodes, incontinence (faecal more specific than urinary), paralysis, or a prolonged period of disorientation afterwards all suggest seizure.
- *Arrhythmia:* an absent or minimal prodrome, preceding palpitations or chest pain, and dramatic collapse suggest arrhythmia.
- *Syncope:* a clear precipitating event (e.g. pain, emotion), description of 'clouding in', and realization of 'going to faint' suggest reflex syncope.
- *Other questions:* are symptoms postural? Carefully review medications for BP-lowering and QT-prolonging drugs.
- Examination may reveal important cardiac findings.
- Check lying and standing BP. A drop in SBP ≥20mmHg or DBP ≥10mmHg is significant.

Box 3.18 Features suggestive of high-risk (serious underlying condition) or low-risk (benign condition) syncope

History features

Low risk	• Typical prodrome suggestive of reflex syncope • Precipitating event (e.g. unpleasant sight or smell) • Prolonged standing • During or immediately after a meal • Triggered by ↑ thoracic pressure (e.g. coughing) • Associated with pressure on carotid sinus • Standing from sitting/lying position
High risk	• New chest pain, dyspnoea, abdominal pain, or headache • Exertional syncope • Syncope while lying down • Palpitations followed by syncope

Past medical history

Low risk	• Long-standing history (years) with low-risk features • Absence of structural heart disease
High risk	• Structural heart disease[*] • Coronary artery disease

Physical examination

Low risk	• Normal examination
High risk	• Unexplained systolic BP <90mmHg • Signs of gastrointestinal bleeding • Persistent bradycardia (<40bpm) • Undiagnosed systolic murmur

ECG[*]

Low risk	• Normal ECG
High risk[**]	• ECG features of acute ischaemia • Mobitz type II second-degree atrioventricular block or complete heart block • Persistent sinus bradycardia (<40bpm) • Repetitive sinoatrial block or sinus pauses (>3s) • Bundle branch block, intraventricular conduction disturbance, ventricular hypertrophy, or Q waves consistent with ischaemic heart disease/cardiomyopathy • Sustained or non-sustained ventricular tachycardia • Dysfunction of an implantable cardiac device • Type 1 Brugada pattern • QTc >460ms in repeated 12-lead ECGs suggestive of long QT syndrome

[*] No prodrome, prodrome <10s, family history of sudden cardiac death at a young age, or syncope while sitting are additional high-risk features if structural heart disease/abnormal ECG.

[**] Mobitz type I second-degree atrioventricular (AV) block, first-degree AV block with markedly prolonged PR interval, asymptomatic mild sinus bradycardia or slow atrial fibrillation (AF), paroxysmal supraventricular ventricular tachycardia or AF, pre-excitation, short QTc, atypical Brugada patterns, and ECG features of arrhythmogenic right ventricular cardiomyopathy are additional high-risk features if the history is consistent with arrhythmic syncope.

Source: data from Brignole M, *et al*. 2018 ESC guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2019;**39**:1883–1948.

Syncope investigations

12-lead ECG	Arrhythmia or heart block may be present Long QT, pre-excitation, Brugada (consider flecainide/ajmaline infusion) are rare causes but may be apparent Q waves, absent R wave, T wave abnormalities, BBB, and LVH all suggest underlying structural heart disease
Exercise ECG	Indicated for exercise-related symptoms or where ischaemia is suspected
Transthoracic echocardiography	Indicated if structural heart disease is suspected. ↓ LV function predicts malignant arrhythmias and risk of SCD. Further investigations (e.g. TOE, CMR, CTCA) may be indicated
Carotid sinus massage	Simple to perform and may be diagnostic in elderly patients (see Box 3.16) Profound bradycardia/asystole (>3s) or ↓ SBP >50mmHg suggested by carotid sinus hypersensitivity Carotid sinus syncope confirmed if massage is positive and reproduces symptoms, and patient history is compatible with reflex syncope
Ambulatory (Holter) monitoring	24h recording has a low yield for identifying arrhythmia. A negative tape has no value if there are no symptoms during the investigation In those with ↓ LVEF, this cannot exclude VT Longer recordings (e.g. 2 weeks) ↑ yield
Implantable loop recorder	For infrequent episodes (less than once a month). Implanted under local anaesthesia Continually records heart rhythm in a loop of 5–10min but stores in memory when activated by the patient (e.g. after a syncopal episode)
Head-up tilt testing	Can be considered if reflex syncope is suspected Patients tilted at 60–80° for 45min If no symptoms, provocation can be given with GTN or isoprenaline Positivity rate depends on patient selection
Electrophysiology study	Rarely indicated for undiagnosed, but strongly suspected, arrhythmia Failure to induce VT indicates ↓, but not absent, risk of events and therefore is of little value in determining the risk of SCD/need for an ICD

For evaluation of the syncopal patient, see Fig. 3.13.

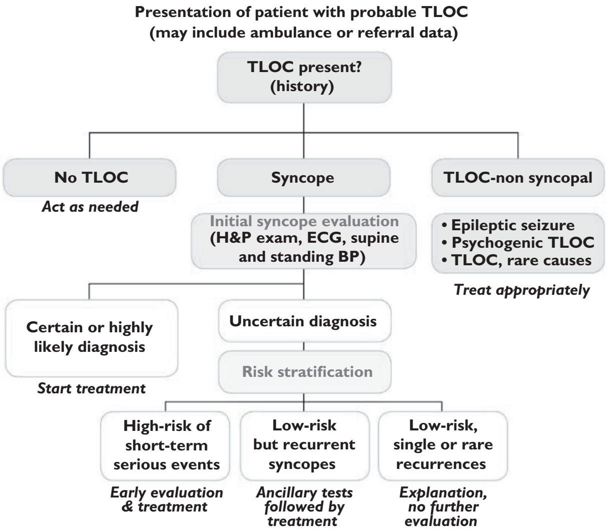
Presentation of patient with probable TLOC
(may include ambulance or referral data)
TLOC present?
(history)
No TLOC
Act as needed
Syncope
TLOC-non syncopal
Initial syncope evaluation
(H&P exam, ECG, supine and standing BP)
• Epileptic seizure
• Psychogenic TLOC
• TLOC, rare causes
Treat appropriately
Certain or highly likely diagnosis
Start treatment
Uncertain diagnosis
Risk stratification
High-risk of short-term serious events
Early evaluation & treatment
Low-risk but recurrent syncopes
Ancillary tests followed by treatment
Low-risk, single or rare recurrences
Explanation, no further evaluation

Fig. 3.13 Evaluation of the syncopal patient.

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Syncope: management

Where a specific cause or precipitation is identified, this should be treated or avoided (e.g. pacing for heart block).

Structural heart disease

Patients with syncope and poor LV function need referral to a cardiologist for consideration of ICD, as there is a risk of sudden death

Neurally mediated 'reflex' syncope

- *Conservative:* lifestyle advice on avoiding precipitating events (such as prolonged standing) and good hydration may be sufficient.
- *Medications:* fludrocortisone (to expand intravascular volume) can be considered in those with vasovagal syncope and low-normal BP values (ESC Class IIb recommendation). Midodrine (α-adrenoceptor agonist) can be considered in those with orthostatic vasovagal syncope (ESC Class IIb recommendation). Use of paroxetine (suggested to interfere with the autonomic reflex arc centrally) or β-blockers (to block LV stretch receptors) is not recommended. Antihypertensives should be stopped or reduced.
- *Pacemakers:* the use of pacemakers (dual chamber with specific rate drop detection algorithms) remains controversial. This may be appropriate if asystole is the dominant feature of reflex syncope.

Driving

Syncope is a condition that may require driving restrictions. This is dependent on the patient, underlying diagnosis, and license type. It is recommended that the Driver and Vehicle Licensing Agency (🖱 www.gov.uk/government/organisations/driver-and-vehicle-licensing-agency) document on driving restrictions with medical conditions is checked if in the UK. If not in the UK, please check local regulations.

Inherited arrhythmia syndromes

This group of diseases attracts public interest because of SCD in otherwise healthy young people. The care of patients and affected families has developed into a multidisciplinary subspecialty, involving cardiologists, geneticists, and pathologists. There is an overlap with inherited disorders of heart muscle. This section focuses on those conditions with a primary electrical problem, predominantly genetic ion channel disorders.

Long QT syndrome

- *Definition:* long QT syndrome (LQTS) is an autosomal dominant (AD) condition characterized by ↑ QT interval on the surface ECG. Predisposes to ventricular arrhythmias, syncope, and SCD. The disease may present in fetal life, although genetically affected individuals may remain asymptomatic lifelong.
- *Epidemiology:* LQTS affects ~1:2500 of the population.
- *Aetiology:* at a molecular level, genetically encoded mutations in either Na$^+$ or K$^+$ channels lead to delayed ventricular repolarization, and hence QT prolongation. The genes encoding both K$^+$ and Na$^+$ channels have been identified, enabling a better understanding of the transition from genetic and molecular anomalies to cardiac phenotype.
- *Diagnosis:* corrected QT interval ≥480ms on repeated ECGs, LQTS score >3 (see Box 3.19), a confirmed LQTS genetic mutation, or unexplained syncope with a corrected QT interval ≥460ms.[1]

Box 3.19 LQTS score

ECG findings

1.	QT interval	
a.	460–470ms	2
b.	≥450ms (in ♂)	1
2.	Torsades de pointes	2
3.	wave alternans	1
4.	Notched T wave in three leads	1
5.	Low heart rate for age	0.5

Clinical history

1.	Syncope	
a.	With stress	2
b.	Without stress	1
2.	Congenital deafness	0.5

Family history

1.	Family members with definite LQTS	1
2.	Unexplained SCD <30 years old in first-degree relative	0.5

LQTS, long QT syndrome; SCD, sudden cardiac death.

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Cellular pathology

Initial depolarization (phase 0) of the cardiac action potential (AP) is determined by rapid Na$^+$ influx (I_{Na}), whereas K$^+$ efflux governs repolarization. K$^+$ channel mutations lead to a loss of channel function and hence delay repolarization and restoration of the resting myocyte voltage through slowed K$^+$ efflux. Conversely, gain-of-function mutations within the Na$^+$ channel facilitate persistent late, slow I_{Na}, and thereby prolongation of depolarization and delayed repolarization. Delayed repolarization manifests on the surface ECG as prolongation of the QT interval. QT prolongation and associated after-depolarizations during critical periods in ventricular repolarization may precipitate TdP (see Fig. 3.14), a polymorphic VT that is the hallmark arrhythmia of QT prolongation.

Congenital LQTS

Congenital LQTS was previously subdivided into two syndromes:

- *Romano–Ward syndrome (RWS):* AD (accounts for 99% of LQTS), causing LQTS without affecting any other organ
- *Jervell–Lange–Nielsen syndrome (JLNS):* much rarer autosomal recessive, associated with sensorineural deafness and a severe cardiac phenotype.

This classification has now been superseded by LQTS subtypes based on associated genetic and channel mutations (see Table 3.7). RWS is genetically LQT1–6 and 9–16. JLNS is forms of LQT1 and LQT5.

Clinical features

Classically associated with syncope or cardiac arrest (due to ventricular arrhythmias). LQT1 is precipitated by exercise (e.g. swimming), whereas in LQT2, symptoms relate to sudden emotional or auditory stimuli, especially if suddenly waking from sleep. Women with LQT2 experience an increase in symptoms in the first 9 months post-partum. Conversely, symptoms in LQT3 are typical at lower HRs during sleep and rest, and although the frequency of symptoms is lower, the rate of sudden death is much higher. Symptoms of LQTS can be misdiagnosed as epilepsy, vasovagal syncope, or breath-holding attacks, with potentially fatal outcomes (SCD).

Acquired LQTS

(See Table 3.7.) QT prolongation may result from cranial trauma, severe hypothermia, electrolyte disturbance, bradycardia, and numerous pharmacological agents. These features may precipitate ECG changes and symptoms in patients with latent congenital LQTS. All patients with the congenital form of the disease should be given a list of drugs that must be actively avoided (🖱 www.crediblemeds.org/).

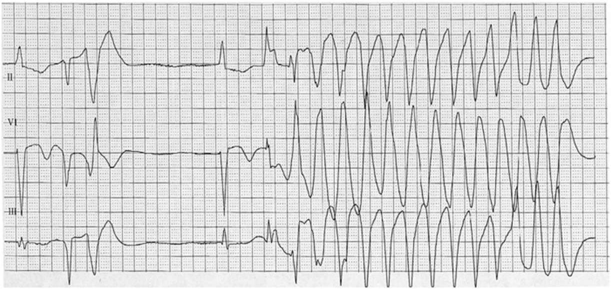

Fig. 3.14 Torsades de pointes. A continuous tracing from three leads of a patient monitored on the coronary care unit. The first complex is a sinus beat followed by two ectopics. There is then a long pause (2s), followed by another junctional beat.

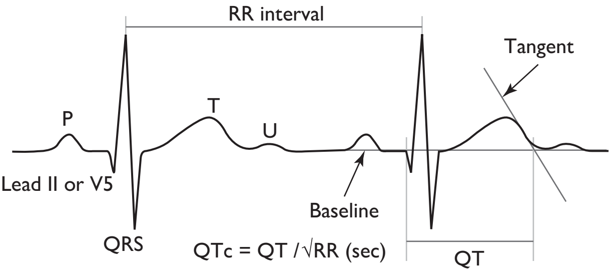

Fig. 3.15 QT interval is measured in lead II or V5 from the point of the first deflection from the baseline of the QRS complex to the end of the T wave, defined as the intersection of the baseline and a tangent drawn to the steepest slope of the descending T wave.

Reproduced from Postema *et al*. *Heart Rhythm* 2008; **5**: 1015–18 with permission from Elsevier.

Investigation and risk stratification

The diagnosis of LQTS is based on the clinical history and ECG. The QT interval should be measured in lead II or V5, and should be corrected for HR according to Bazett's formula [$QTc = QT/\sqrt{(RR)}$] or Fridericia [$QTcf = QT/\sqrt[3]{(RR)}$] (see Fig. 3.15). Risk stratification is based on age, sex, QT interval, recent symptoms, and genetic diagnosis.

Reference

1. Zeppenfeld K, Tfelt-Hansen J, de Riva M, *et al*.; ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;**43**:3997–4126.

Long QT syndrome (continued)

Table 3.7 Characteristics of currently identified congenital LQTS

LQTS	Mutation	Ion current	Prevalence	Clinical features
1	*KCNQ1*	I_{ks}	40–55% of cases	Exercise-related syncope
2	*KCNH2*	I_{kr}	30–45% of cases	Syncope related to sudden emotional or auditory stress
3	*SCN5A*	I_{Na}	5–10% of cases	Symptoms at rest (NB LQT1). Young age, usually presents as SCD
4	*Ankyrin-B*	–	<1%	Highly variable phenotype
5	*KCNE1*	I_{ks}	<1%	–
6	*KCNE2*	I_{kr}	<1%	–
7 (Andersen syndrome)	*KCNJ2*	I_{kr}	200 cases worldwide	Associated with periodic paralysis
8 (Timothy syndrome)	*CACNAIC*	I_{Ca}	<20 cases worldwide	Cardiac structural abnormalities and autism spectrum
9	*CAV3*	I_{Na}	<1%	–
10	*SCN4B*	I_{Na}	<1%	–
11	*AKAP9*	–	<1%	–
12	*SNTA1*	I_{Na}	<1%	–
13	*KCNJ5*	I_{kr}	<1%	–

Common causes of acquired LQTS

Drugs

- *Antiarrhythmics:* quinidine, procainamide, disopyramide, flecainide, propafenone, sotalol, ibutilide, dofetilide, amiodarone (rare).
- *Antimicrobials:* erythromycin, clarithromycin, trimethoprim, ketoconazole, itraconazole, chloroquine.
- *Antihistamines*: terfenadine.
- *Other drugs*: amitriptyline, fluvoxamine, chlorpromazine, domperidone, cisapride, glibenclamide.

NB this is not a comprehensive list. When a patient is known to be at risk of LQTS, all drugs and potential interactions should be checked. CredibleMeds (🖱 www.crediblemeds.org) contains an up-to-date list of QT-prolonging medications.

Electrolyte imbalance

- Hypokalaemia, hypomagnesaemia, hypocalcaemia.

Severe bradycardia

- CHB, SAN disease, hypothyroidism, hypothermia.

Long QT syndrome: management

Acute management of torsades de pointes

TdP usually terminates spontaneously, although it may degenerate to VF. A prolonged episode with CV compromise needs immediate DCCV. For recurrent bursts or following cardiac arrest, use IV Mg^{2+} bolus and infusion, followed by urgent temporary pacing (at a rate of 90–110/min) if necessary.

Acquired LQTS

In acquired LQTS, TdP risk is ↑ by bradycardia due to higher chances of an after-depolarization occurring during repolarization.

1. The underlying cause should be identified and reversed.
2. Stop offending drugs.
3. Give Mg^{2+} before getting blood results.
4. K^+ can be checked rapidly with a blood gas; replace if <4mmol/L, and aim to achieve high normal levels.
5. An isoprenaline infusion can be commenced while waiting to pace.
6. Long-term treatment is not usually necessary; however, a permanent pacemaker is required if non-reversible heart block is found.

Congenital

General lifestyle advice

- QT-prolonging drugs should be avoided.
- Electrolytes should be corrected promptly (e.g. following diarrhoea, vomiting, or metabolic conditions).
- Avoid genotype-specific triggers for arrhythmias (see Box 3.20).

Box 3.20 Genotype-specific arrhythmic triggers in LQTS

- *LQTS1:* strenuous exercise (particularly swimming)
- *LQTS2:* loud noises
- *LQTS3:* events are often precipitated by sleep/rest. However, this cannot be avoided.

Medical and device therapy

As most events are triggered by sudden ↑ of sympathetic activity, treatment is aimed at preventing this.

β-blockade

- This is the mainstay and is especially effective in LQT1, although less so in LQT3.
- Recommended in patients with a clinical diagnosis of LQTS.
- Should be considered in those with long QT-causing genetic mutations with normal QT intervals.

Implantable cardioverter–defibrillators

- Should only be used with careful consideration. ICDs prevent SCD, but not TdP, and recurrent distressing shocks for non-sustained episodes can ruin a patient's life.

- Careful patient selection, concomitant use of β-blockers, and appropriate device programming minimize inappropriate therapies.
- Recommended in those with LQTS who have had a previous cardiac arrest.
- Should be considered in those who have syncope/VT while on β-blockers.

Other therapies

- In resistant cases, or where ICD is contraindicated and/or β-blockers are not tolerated, left cardiac sympathectomy may be effective.
- Na^+ channel blockers (e.g. flecainide) may be considered as adjuvant therapy in those with LQTS3.

Asymptomatic patients

- Once a diagnosis of LQTS has been made, screening should be offered to all first-degree family members.
- Screening (clinical and/or genetic) of families reveals patients with LQTS who have never had symptoms and may have a normal QTc.
- All patients must be carefully evaluated, and risks determined on an individualized basis. Most patients do not die from LQTS, but all are at risk (13% incidence of fatal events over a lifetime if untreated).
- A balance must be struck between lifelong treatment with side effects and the spectre of sudden death.

Treatment of asymptomatic patients

- β-blockers are recommended in those with a diagnosis of LQTS, even if asymptomatic.
- In those with a pathogenic *KCNH2* or *SCN5A* mutation, ICD implantation, in addition to β-blocker therapy, may be considered, even if asymptomatic.

Short QT syndrome

- *Definition:* a genetic disorder leading to shortening of the repolarization period of the ventricle and ↑ the risk of ventricular arrhythmias.
- *Epidemiology:* this condition is very rare. As a result, accurate data on prevalence are not available.
- *Aetiology:* five genes have been implicated in this condition relating to K^+ and Ca^{2+} channels. However, only 20% of those with short QT syndrome (SQTS) have an established genetic defect.
- *ECG features:* a corrected QT interval below normal limits.
- *Presentation:* cardiac arrest is the most common presenting feature. Other common symptoms include syncope and palpitations. AF is commonly found in those with SQTS.
- *Outcomes:* >40% of affected individuals have a cardiac arrest by the age of 40 years.
- *Diagnosis:* a corrected QT interval of <340ms in men and <330ms in women is diagnostic in asymptomatic individuals. In those with a family history or with symptoms, then a corrected QT interval of <360ms in men and ≤370ms in women is considered diagnostic.
- *Treatment*:
  - ICDs should be offered to all those with SQTS who are survivors of a cardiac arrest or who have documented sustained VT.
  - Quinidine or sotalol can be considered in those with SQTS requiring an ICD but have contraindications or refuse an ICD implant. These agents can also be considered in those who are asymptomatic but have a family history of SCD.

Brugada syndrome

- *Definition:* genetic disorder leading to ECG changes and ↑ risk of SCD.
- *Epidemiology:* prevalence between 0.01% and 0.3%. The disease is especially prevalent in South East Asian individuals and shows both age- and sex-related penetrance, classically presenting in ♂ (♂:♀ 8:1) in their 30s and 40s. Up to 1% of adults have a Brugada-type ECG pattern but remain asymptomatic for life.
- *Aetiology:* AD genetic disorder. ~20% of patients will have identifiable mutations in the Na^+ channel gene (*SCN5A*). Multiple other ion channel mutations have been identified. The range of mutations explains the variable presentation.
- *ECG features:* characterized J-point elevation of >2mm in leads V1–V3. There are three distinct patterns of ECG changes (see Box 3.21).

Box 3.21 ECG changes in Brugada syndrome

- *Type 1 pattern*: coved ST-segment elevation >2mm and inverted T wave in leads V1 and/or V2
- *Type 2 pattern*: saddle-back ST-segment elevation ≥1mm
- *Type 3 pattern*: saddle-back/coved ST-segment elevation <1mm

- *Presentation:* syncope occurs in 30% of those with Brugada syndrome (BrS) and VF leading to cardiac arrest, although ECG findings may be incidental.
- *Outcomes:* hypothesized to be a cause of 4–12% of SCDs.

- *Diagnosis:* this is based on ECG findings.
  - Spontaneous type 1 pattern in ≥1 anterior (or high) precordial leads (V1–V3) is diagnostic.
  - ECG may be precipitated by fever and medications, including class 1 antiarrhythmics, antidepressants, antipsychotics, and cocaine.
  - Type 2/3 patterns are non-diagnostic, but suggestive. May convert to a type 1 pattern with a pharmacological challenge (see Box 3.22).
  - If strongly suspected, leads V1 and V2 can be placed in the third or second intercostal space, which ↑ diagnostic sensitivity.
- *ECG differentials:* conditions that should be actively excluded are atypical RBBB, acute MI, pericarditis, ARVC, and autonomic and electrolyte disturbances.
- *Treatment:* patients with symptomatic BrS (syncope, VT, VF) should undergo ICD implantation. Quinidine should be considered to treat electrical storms and in patients who qualify for an ICD but have contraindications, or when patients refuse.
- *Lifestyle changes:* drugs which induce ST-segment elevation in right precordial leads should be avoided (🖱 www.brugadadrugs.org). Excessive alcohol should be avoided. Fevers should be treated promptly with antipyretics.

Box 3.22 Pharmacological challenge for Brugada syndrome

Potential indications

- Patients with non-diagnostic type 2 or type 3 ECGs.
- Patients with a first-degree relative diagnosed with BrS.

Procedure

- Give a class 1a antiarrhythmic agent in an infusion: ajmaline 1mg/kg IV to max. 100mg, or flecainide 2mg/kg IV to max. 150mg (see Fig. 3.16).
- Development of type 1 pattern is a positive test.
- If type 1 pattern develops, stop the infusion. Continue monitoring until the drug is washed out of the system and the ECG has returned to normal.

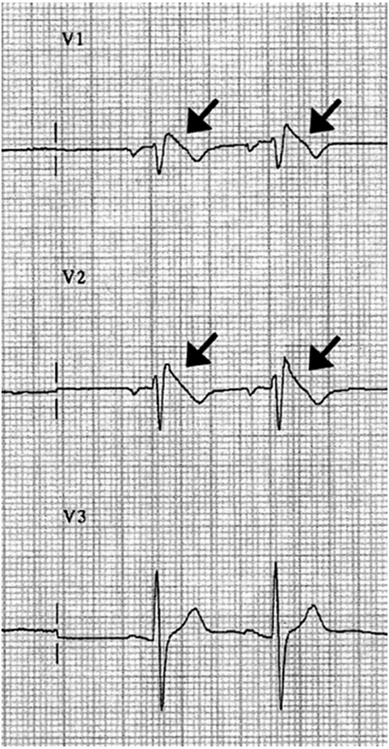

Fig. 3.16 Brugada ECG with flecainide challenge. A typical Brugada ECG with arrows marking the characteristic prominent coved ST-segment elevation in the right precordial leads, ≥2mm at its peak, followed by a negative T wave with little or no isoelectric separation. IV administration of either ajmaline or flecainide exaggerate the ST changes or reveals them if initially absent.

Catecholaminergic polymorphic ventricular tachycardia

Overview

- *Definition:* an aggressive condition characterized by adrenergically stimulated polymorphic VT.
- *Epidemiology:* prevalence estimated at 0.01%.
- *Diagnosis:* catecholaminergic polymorphic VT (CPVT) is defined as a structurally normal heart, with a normal ECG and exercise/emotion-induced bidirectional or polymorphic VT. Alternatively, carriers of mutations in the *RyR2* or *CASQ2* genes.
- *Aetiology:* genetic condition caused by mutations in the ryanodine receptor (AD) or calsequestrin (autosomal recessive), leading to myocardial Ca^{2+} flux abnormalities, which, in the presence of catecholamines, trigger delayed after-depolarizations and VT.
- *Presentation:* patients present with palpitations, syncope, or cardiac arrest during exercise or emotional stimulation, often in the first two decades of life.
- *Screening:* those with a first-degree relative with confirmed CPVT should undergo screening. Where a confirmed mutation is known, this should include genetic screening.
- *Investigations:* baseline ECG and echocardiogram are normal. Investigations include exercise testing, Holter monitoring, and adrenaline provocation, which reveal the classical bidirectional or polymorphic VT (see Fig. 3.17), usually once the HR reaches 110–120bpm. Adrenaline testing is particularly useful in those who cannot exercise.

Management

- Avoid competitive sports, strenuous exercise, and stressful environments.

β-blockers

- These are the mainstay of therapy and are recommended in all patients with CPVT.
- Should also be considered in genetically positive family members, even if exercise testing is negative.

Other medical therapy

- Flecainide can be added to β-blockers in those with CPVT.

ICD implantation

- Given the highly aggressive nature of the disease, ICD implantation should be considered in patients with symptoms or persistent VT despite appropriate drug therapy.
- ICD implantation is additionally recommended in those with CPVT who experience cardiac arrest or recurrent syncope.

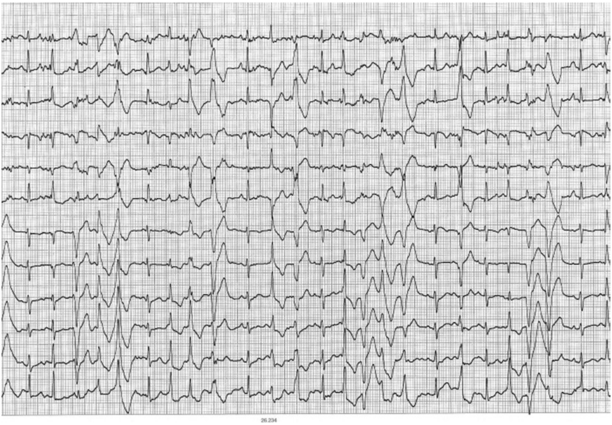

Fig. 3.17 ECG of a patient with CPVT demonstrating bidirectional ventricular ectopic beats/ventricular triplets.

Image courtesy of Dr Chris Miles.

Arrhythmia in special situations

Paediatrics

Arrhythmia may occur at any stage in the paediatric population, from fetal life to adolescence.

Fetus and neonate

AVRT and AFl are the usual cause of tachycardia. If persistent, *hydrops fetalis* may result. The majority of AVRT cases resolve spontaneously *in utero* or by 1 year of age, although recurrences later in life may occur. Ablation is rarely necessary. Congenital heart block occurs mediated by maternal anti-Ro/SSA antibodies and, if severe, may also cause hydrops fetalis. This always persists after birth and usually requires permanent pacing; timing depends on the stability of the subsidiary pacemaker.

Infancy and childhood

AVRT is the usual (80%) cause of tachycardia. AVNRT is rare in infancy but becomes increasingly common in teenage years. Focal ATs and a specific form of AVRT mediated by a slow atrial septal accessory pathway (persistent junctional reciprocating tachycardia) both lead to incessant tachycardia and profound ventricular dysfunction (tachycardia cardiomyopathy). This completely resolves with successful therapy. RFA is now commonly performed in older children and may also be used in refractory arrhythmias in neonates and young infants.

Congenital heart disease

Arrhythmias in association with congenital cardiac lesions are poorly tolerated and, if uncontrolled, may lead to a rapid decline in ventricular function and CO.

Supraventricular tachycardia

This is a major cause of both morbidity and mortality in congenital heart disease. Accessory pathways are associated with Ebstein's anomaly and congenitally corrected transposition of the great arteries, and this results in AVRT. Macro-re-entrant AT is common, late, following the Mustard or Fontan procedure. This is difficult to control with medication, and although ablation (either percutaneous or surgical) is commonly successful acutely, arrhythmia recurrence is a problem.

Ventricular tachycardia

VT is seen in Ebstein's anomaly and following repair of tetralogy of Fallot. Treatment may involve either RFA or an ICD.

Pregnancy

Haemodynamic and hormonal changes associated with pregnancy may unmask arrhythmic substrates for the first time or exacerbate pre-existing arrhythmic conditions. Gestational palpitations are common, and, most frequently, ↑ awareness of physiological tachycardia. If new ventricular arrhythmias occur, peripartum cardiomyopathy should be actively excluded (see ➔ Peripartum cardiomyopathy, p. 418).

Chapter 4

Valvular heart disease

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General considerations

Development

Cardiac valves develop from the mesodermal germ layer between the fourth and seventh week of gestation. Any factors affecting embryogenesis during this time can affect the development of valves and include infection (German measles/rubella), drugs, etc.

Key concepts

Mitral valve

- Two leaflets: anterior (is in fibrous continuity with the aortic valve annulus) and posterior leaflets. Competency depends on a large-zone of coaptation. Supported by the annulus and posteromedial and anterolateral papillary muscles coming off the LV free wall and septum, and tendinae chordae—changes in any of above can result in MR (see Fig. 4.1).
- The posterior leaflet is divided into three segments by scallops. The anterior leaflet is not scalloped. Anterior segments are based on which parts are opposite the posterior scallops.
- The posteromedial papillary muscle is supplied by the posterior descending coronary artery from either the circumflex or RCA and is most prone to ischaemic rupture, causing flail posterior leaflet (compared with the anterolateral papillary muscle, which has dual supply: left anterior descending and circumflex arteries).
- Posterior regurgitant jet is caused by posterior leaflet restriction (common) or anterior leaflet prolapse (unusual), and an anteriorly directed jet is due to posterior leaflet prolapse (most common) or anterior leaflet restriction (unusual). Central leaks come from annular dilatation. Eccentric jets are often caused by commissural prolapse.

Aortic valve

- Trileaflet valve (right and left coronary cusps based on the location of the coronary ostia, and non-coronary cusp), with a small zone of coaptation.
- Increase in size of the annulus, sinuses, sinotubular junction, leaflet prolapse, or leaflet destruction can result in aortic insufficiency (AI).
- Conduction tissue runs between the right and non-coronary cusps.

Tricuspid valve

- Three leaflets (septal, anterior, and posterior), with a moderate zone of coaptation. The posterior and anterior regions of the annulus are most prone to dilatation.
- AVN tissue is located just below the anteroseptal commissure.

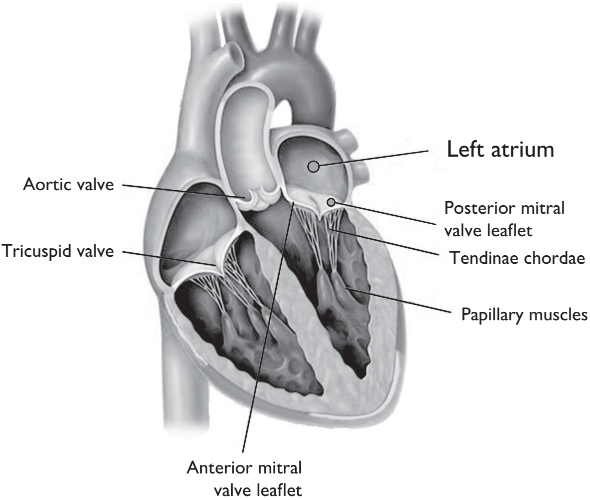
Left atrium
Aortic valve
Posterior mitral valve leaflet
Tricuspid valve
Tendinae chordae
Papillary muscles
Anterior mitral valve leaflet

Fig. 4.1 Diagram showing the anatomical location of the mitral, aortic, and tricuspid heart valves.

Acute rheumatic fever

Epidemiology

- <1:1000 in developed countries; 10:1000 schoolchildren in developing countries. It is rarer but still accounts for half of cardiac disease in the developing world.
- Declining incidence due to improved economic standards and housing, ↓ crowding and access to medical care/antimicrobials.
- Typically affects children aged 5–15 years from lower socio-economic class living in crowded conditions; 20% of cases are among adults. Incidence is higher in native Hawaiians and Maoris despite antibiotic prophylaxis.
- No sex difference in acute rheumatic fever (ARF), but chorea and MS are more common in ♀.

Pathophysiology

- Typically occurs several weeks after streptococcal pharyngitis. Usually group A β-haemolytic streptococci: *Streptococcus pyogenes* serotype M. Antigenic mimicry is implicated—antibodies to carbohydrate in cell wall (anti-M antibodies) of group A *Streptococcus* cross-react with protein in cardiac valves.
- Delay from acute infection to onset of ARF is usually 3–4 weeks. ARF is thought to complicate up to 3% of untreated streptococcal sore throats. Previous episodes of ARF predispose to further events (up to 50% of cases of streptococcal sore throat are complicated by ARF if there has been a previous episode). Other areas of cross-reactivity may explain other signs (e.g. connective tissue in joints—arthritis; caudate nucleus in the brain—Sydenham's chorea).
- Commonly causes pancarditis. Pericarditis can cause haemodynamic instability or constriction. Myocarditis may cause acute HF and arrhythmias. Endocarditis affects the MV (65–70%), aortic valve (25%), and tricuspid valve (10%, never in isolation), causing acute regurgitation and HF, and eventually chronic stenosis.
- The pericardium and myocardium develop perivascular foci of eosinophilic collagen surrounded by lymphocytes, plasma cells, and macrophages called Aschoff bodies.
- Sixty per cent of those in communities where ARF is endemic will subsequently develop rheumatic heart disease (RHD)—less likely in developed countries.

Clinical features

- *Sore throat* 1–5 weeks earlier is reported in two-thirds of cases.
- Fever, abdominal pain, and epistaxis.
- Migratory large joint *polyarthritis* starting in the lower limbs in 75% of cases. Duration of <4 weeks at each site. Severe pain and tenderness in contrast to degree of joint swelling.
- *Pancarditis* in 50% of cases, with features of acute HF, MR and AR, an apical, mid-diastolic flow murmur (Carey Coombs murmur), and pericarditis.
- *Chorea* in 10–30%, usually 1–6 months after pharyngitis. Difficulty with writing and speaking, generalized weakness, choreiform movements,

and emotional lability. Joints hyperextended, with hypotonia, diminished tendon reflexes, tongue fasciculation, and a relapsing grip (alternate ↑/↓ in tension). Recovery over 2–3 months.

- *Erythema marginatum* is an evanescent rash with serpiginous margins and central clearings on the trunk and proximal limbs. Seen in 5–13% of cases. Begins as erythematous, non-pruritic papules/macules that spread outwards. Fades and reappears over hours and persists.
- *Subcutaneous nodules* in 0–8% of cases several weeks after the onset of severe pancarditis. Mainly over bony surfaces or prominences and tendons. Commonly involves the elbows, knees, wrists, ankles, Achilles tendons, occiput, and vertebral spinous processes. Duration of 1–2 weeks.
- ARF may be overdiagnosed in children admitted with fever, soft murmurs, and arthralgia, which are common in childhood (see Box 4.1).

Box 4.1 Diagnosis of rheumatic fever (Jones criteria)

Evidence of group A streptococcal pharyngitis

Either a positive throat culture or rapid streptococcal antigen test, or an elevated or rising streptococcal antibody titre (samples taken 2 weeks apart)

Plus two major or one major and two minor criteria

Major criteria	Minor criteria
• Polyarthritis	• Fever
• Carditis	• Arthralgia
• Chorea	• Prolonged PR interval
• Erythema marginatum	• Elevated ESR and CRP
• Subcutaneous nodules	

Management

Management of current infection

- Streptococcal sore throat should be managed with antibiotics to prevent ARF from developing (see Table 4.1). Local guidelines should be consulted; Table 4.1 shows AHA recommended regimens. Once ARF has developed, antibiotic treatment has no effect on the course of the current attack and does not affect cardiac involvement.

Management of acute attack

- *Arthralgia:* aspirin should be used for arthralgia analgesia. Up to 80–100mg/kg/day in 4–5 divided doses. In children, due to Reye's syndrome, aspirin should be held during intercurrent viral infections.
- *Carditis:* prednisolone previously recommended in moderate to severe carditis, but there is no evidence of reduction of progression to RHD. Carditis resulting in HF should be treated.
- *Sydenham's chorea:* treatment only required in severe cases, as chorea is normally self-limiting. Carbamazepine and sodium valproate have similar efficacy.

Table 4.1 Antibiotic treatment of rheumatic fever

Drug/treatment	Route	Duration	Dose
Phenoxymethylpenicillin	PO	10 days	*Children:* 250mg four times daily (qds) *Adults:* 500mg three times daily (tds)
Benzylpenicillin	IM	One dose	1.2 million units
Azithromycin	PO	5 days	*Children:* 12mg/kg od *Adults:* 500mg qds

Alternatives include clarithromycin, erythromycin, and cefalexin.

Source: data from: Gerber MA, *et al*. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal Pharyngitis. *Circulation*. 2009;**119**:1541–51.

Prophylaxis against further attacks

- Future group A streptococcal infections should be avoided.
- Regular prophylaxis with benzylpenicillin 900mg intramuscularly (IM) every 3–4 weeks is recommended where compliance is an issue.
- Alternatively, PO phenoxymethylpenicillin 250mg bd (or a macrolide if penicillin-allergic). Duration depends on the severity of ARF (see Table 4.2).

Table 4.2 Secondary prophylaxis duration following acute rheumatic fever

Condition	Duration (whichever longer)
No carditis or valvular disease	Until 21 years old OR For 5 years
Documented carditis from no valvular disease	Until 21 years old OR For 10 years
Carditis and persistent valvular heart disease	Until 40 years old OR For 10 years Lifelong prophylaxis may be needed

Source: data from: Gerber MA, *et al*. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal Pharyngitis. *Circulation*. 2009;**119**:1541–51.

Prognosis

- ARF recurrence is highest in the first years after the initial episode.
- Progression to RHD dependent on the degree of cardiac involvement and appropriate secondary prophylaxis. Chronic valve disease occurs in one-third of cases without, and in two-thirds of cases with, recurrence.
- Acute phase duration of about 3 months in 80% of cases. Mortality of 1–10% in developing countries.
- Murmurs resolve in 50% of cases up to 5 years after index infection.

Mitral stenosis: overview

Aetiology

- MS is usually secondary to rheumatic fever. Incidence ↓ due to reduced incidence of ARF.
- Rare causes include congenital (isolated lesion or in association with an ASD—Lutembacher's syndrome), mitral annular calcification, carcinoid heart disease, valvulitis (systemic lupus erythematosus), mucopolysaccharidoses (e.g. Hurler's syndrome), and endocardial fibroelastosis.
- Stenosis occurs at three levels: the chordae (fuse, thicken, then shorten); cusps (initially rolled under edges, then thicken and eventually calcify); and commissures (progressive fusion).

Pathophysiology

- *Elevated LA pressure:* required to propel blood through the narrowed valve orifice. Leads to raised pulmonary venous pressure and exertional dyspnoea due to pulmonary oedema.
- *PHT:* occurs due to raised LA pressure; leads to RV hypertrophy (RVH) and failure.
- *LV function:* initially unaffected. However, since filling is impaired, adequate CO cannot always be maintained. The rise in CO during exertion is blunted.
- *AF:* onset is associated with abrupt clinical deterioration, due to both loss of atrial systole and fast HR (↓ duration of diastole).

Clinical features

History

- *Breathlessness:* dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea. Pulmonary oedema may be precipitated by uncontrolled AF, exercise, chest infection, anaesthesia, or pregnancy.
- *Palpitations:* thromboembolism risk (occurs in 20–30%) ↑ by AF. Emboli usually originate in the dilated LA/LA appendage.
- *Fatigue:* due to reduced CO reserve and common in mild to moderate stenosis.
- *Haemoptysis:* can occur for a variety of reasons: alveolar capillary rupture (pink, frothy pulmonary oedema); bronchial vein rupture (larger haemorrhage); bloodstained sputum of chronic bronchitis; pulmonary infarction (low CO, immobile patients).
- *Chest pain:* similar to angina, may occur in patients with PHT and RVH, even with normal coronaries.
- *Hoarse voice (rarely):* the enlarging LA may compress surrounding structures, producing a hoarse voice (left recurrent laryngeal nerve compression—Ortner's syndrome). Compression may also cause dysphagia (oesophagus) or left lung collapse (left main bronchus).

Physical examination

(See Fig. 4.2)

- *Mitral facies or malar flush:* seen in <50%.
- *JVP:* classically prominent 'a' waves.
- *Pulse:* low-amplitude arterial pulse. Irregularly irregular in AF.

- *Apex beat:* 'tapping' palpable S_1.
- *Cardiac palpation:* diastolic thrill at the apex, left parasternal heave (due to RVH), and palpable pulmonary closure.
- *Auscultation:* S_1 loud if in SR and valve is pliable. P_2 accentuated due to PHT. MV opening snap (OS) is heard best in expiration at, or medial to, the apex. A_2–OS interval varies inversely with severity of stenosis. Low-pitched, rumbling mid-diastolic murmur with presystolic accentuation (if in SR) is heard best at the apex with the patient in the left lateral position. Early diastolic murmur due to pulmonary regurgitation (PR) from PHT (Graham Steell murmur) may be heard rarely.

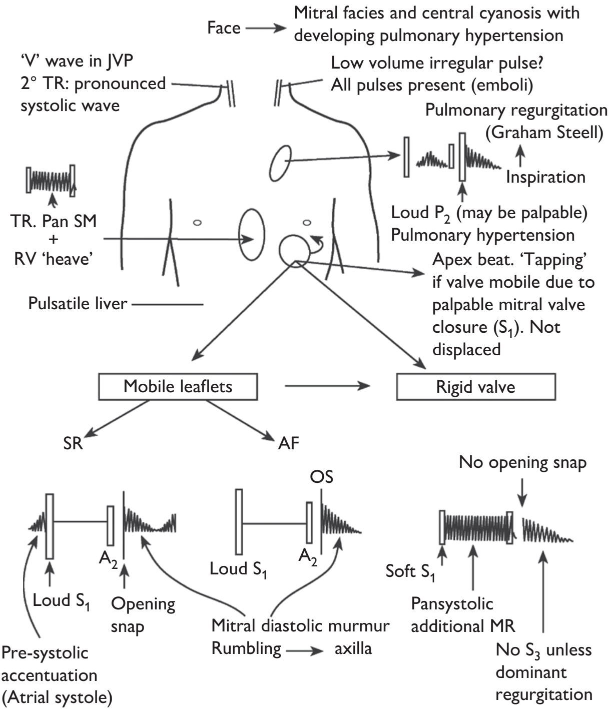
Face
Mitral facies and central cyanosis with developing pulmonary hypertension
'V' wave in JVP
2° TR: pronounced systolic wave
Low volume irregular pulse?
All pulses present (emboli)
Pulmonary regurgitation (Graham Steell)
Inspiration
TR. Pan SM + RV 'heave'
Loud P_2 (may be palpable)
Pulmonary hypertension
Apex beat. 'Tapping' if valve mobile due to palpable mitral valve closure (S_1). Not displaced
Pulsatile liver
Mobile leaflets
Rigid valve
SR
AF
OS
No opening snap
A_2
Loud S_1
Opening snap
Loud S_1
A_2
Soft S_1
Pansystolic additional MR
Mitral diastolic murmur
Rumbling → axilla
Pre-systolic accentuation (Atrial systole)
No S_3 unless dominant regurgitation

Fig. 4.2 Physical signs in mitral stenosis. AF, atrial fibrillation; JVP, jugular venous pressure; MR, mitral regurgitation; OS, opening snap; RV, right ventricular; SM, systolic murmur; SR, sinus rhythm; TR, tricuspid regurgitation.

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Mitral stenosis: investigations

- *ECG:* bifid P wave (if in SR) due to LA enlargement, most prominent in lead II. Tall and peaked P waves in PHT. AF is frequent. Right axis deviation and RVH.
- *CXR:* straightening of the left heart border, prominent upper lobe veins, PA enlargement, Kerley B lines—interstitial oedema. Large LA visible as a double shadow (see Box 4.2).

Box 4.2 Radiographic features of mitral stenosis

Posteroanterior film

- Straight or convex left heart border
- Double shadow of left atrium behind right atrium
- Splaying of carina (>90°)—rare
- Dilated upper lobe veins
- Prominent pulmonary conus
- Patchy perihilar or basilar alveolar infiltrates suggestive of pulmonary haemosiderosis

Lateral film

- LA or RV enlargement
- Valvular calcification frequent
- LA calcification seen rarely (McCallum's patch)
- Oesophageal indentation on barium swallow

- *TTE:* the parasternal long-axis view (PLAX) shows enlarged LA and doming of the valve leaflets due to commissural fusion. In the short-axis view (SAX), the MV orifice can be calculated by planimetry. Calcification can be visualized. M-mode imaging—restricted valve leaflet separation due to commissural fusion. Continuous-wave (CW) Doppler can be used to estimate the valve area and transvalvular gradient (see ➔ TTE: Doppler, pp. 490–1). Valve echo score can be calculated (see Table 4.3).
- *TOE:* provides better anatomical detail; can visualize small vegetations and thrombi in the LA.
- *Cardiac catheterization:* ↑ PCWP. ↑ PCWP to LV end-diastolic pressure gradient. If the mean mitral gradient is low at rest, get the patient to perform exercise on the cath-lab table (e.g. straight leg raising) to calculate the gradient again. Assessment of coexisting coronary and valvular lesions.

Table 4.3 Classification of mitral stenosis

Severity	Mean gradient (mmHg)	PA systolic (mmHg)	Valve area (cm^2)
Mild MS	<5	<30	>1.5
Moderate MS	5–10	30–50	1–1.5
Severe MS	>10	>50	<1

PA , pulmonary artery; MS, mitral stenosis.

Mitral stenosis: management

Medical management

- *Mild symptoms:* salt intake restriction and PO diuretics (cautious).
- *In AF*: digoxin, β-blocker, or CCB for rate control. Restoration of SR may be attempted if appropriate.
- *Anticoagulation:* recommended for those with additional risk factors (see Box 4.3). DOACs should NOT be used in this setting.
- Endocarditis prophylaxis is no longer recommended.

Box 4.3 Indications for anticoagulation in mitral stenosis

ESC Class I recommendation

- Concomitant atrial fibrillation
- Previous systemic embolism
- Thrombus in left atrium

ESC Class IIa recommendation

- Dense spontaneous contrast in left atrium on transoesophageal echocardiography
- Left atrial volume >60mL/m^2

Determining when to intervene

- Patients with severe MS and symptoms should have intervention (ESC Class I recommendation).
- If asymptomatic and at ↑ risk of embolism/decompensation (see Boxes 4.3 and 4.4), the patient should be considered for intervention (ESC Class IIa recommendation).
- Asymptomatic patients at low risk of embolism/haemodynamic decompensation should undergo exercise testing. If truly asymptomatic, a conservative approach can be undertaken (see Box 4.5).

Box 4.4 High-risk features for haemodynamic decompensation

- Pulmonary pressure >50mmHg at rest
- Desire for pregnancy
- Need for major non-cardiac surgery

Box 4.5 Monitoring in mitral stenosis

- *Significant MS:* if asymptomatic, clinical review and TTE yearly
- *Moderate MS:* clinical review and TTE every 2–3 years

Percutaneous mitral commissurotomy

- First-line therapy in patients with symptoms, no contraindications (see Box 4.6), and favourable anatomical characteristics (ideally summed valve score <8; see Table 4.4) (ESC Class I recommendation).
- Percutaneous mitral commissurotomy (PMC) is indicated if symptomatic and high surgical risk (ESC Class I recommendation).
- A guidewire is placed in the LA after trans-septal puncture, and a balloon (Inoue balloon) placed across the valve orifice and inflated.

Box 4.6 Contraindications to percutaneous mitral commissurotomy

- Mitral valve area >1.5cm^2
- Left atrial thrombus
- > mild mitral regurgitation
- Concomitant coronary artery disease requiring bypass surgery
- Absence of commissural fusion
- Severe aortic valve disease, or severe combined tricuspid stenosis and regurgitation requiring surgery
- Severe/bi-commissural calcification

Table 4.4 Summary of Wilkins score for grading mitral stenosis characteristics

Grade	Mobility	Leaflet thickening	Leaflet calcification	Subvalvular thickening
1	Highly mobile	Near normal	Single area of brightness	Minimal chordal
2	↓ mobility	Thickened tips	Scattered at margins	Up to one-third of chords
3	Basal leaflet only	Entire leaflet	Extends to mid leaflets	To distal third of chords
4	Minimal	Marked thickening	Extensive brightness	Extensive and shortened

Source: data from Wilkins T *et al*. *Heart*. 1988;**60**:299–308.

Surgical treatment

- Surgical management should be undertaken when intervention is indicated, there are contraindications to PMC, and there is low surgical risk (ESC Class I recommendation).
- *Closed valvotomy:* fused cusps separated by a dilator introduced through the LV apex. No longer recommended.
- *Open valvotomy:* preferred to closed valvotomy. Cusps are separated under direct vision. Any subvalvular apparatus fusion is loosened.
- *Mitral repair:* occasionally possible in advanced rheumatic stenosis by using the pericardium to augment leaflets, but durability is 5–10 years.
- *MV replacement:* if repair is not possible.
    - Annual risk of major thromboembolic/haemorrhagic event is 2–4% with mechanical valve (so high lifetime risk in young patients), with a small risk of reoperation for valve dysfunction.
    - Bioprosthetic valve durability dependent on patient age: ~75% free from valve degeneration at 15 years if aged <65 years; ~90% free at 15 years if aged >65 years. In those aged >70 years, a bioprosthesis should be considered (ESC Class IIa recommendation).
    - Concomitant surgical ablation for AF has ~60% success at 1 year and should be considered (ESC Class IIa recommendation).
    - Mechanical replacement may be considered when preoperative AF requires anticoagulation (ESC Class IIb recommendation).
- *Risk of surgery:* 1–2% mortality and stroke in 65-year-old patients with no other major morbidity and good LV function.

Mitral regurgitation: overview

Causes

- *Acute:* ruptured chordae, myxomatous degeneration, infective endocarditis, acute MI, trauma.
- *Chronic:* most common—myxomatous degeneration (MV prolapse), RHD, LV or annular dilatation (e.g. ischaemia, cardiomyopathy, annular calcification), degeneration of valve cusps, collagen vascular disease, HCM.

Nomenclature

- There is a spectrum of myxomatous degenerative disease from single-segment prolapse in small valves (fibroelastic deficiency) to multi-segment prolapse in large valves (Barlow's disease).
- MR can be classified based on the mechanism, according to the Carpentier classification (see Box 4.7).

Box 4.7 Carpentier classification

- *Type I:* normal leaflet motion (e.g. dilated annulus from dilated cardiomyopathy, leaflet perforation due to endocarditis)
- *Type II:* leaflet prolapse (e.g. myxomatous degeneration)
- *Type IIIa:* restricted leaflet opening (e.g. rheumatic disease)
- *Type IIIb:* restricted leaflet closing (e.g. ischaemic dilated cardiomyopathy (functional)).

Reproduced from Carpentier A, *Journal of Thoracic and Cardiovascular Surgery* 1983; **86**(3);323–7 with permission from Elsevier.

Pathophysiology

- Leaflets, chordae, papillary muscles, or LV damage can cause MR.
- The LV ejects into the LA in systole, as well as antegradely into the aorta.

Acute mitral regurgitation

- There is little enlargement of the LA due to normal compliance.
- Results in raised LA pressure and can result in pulmonary oedema.
- There is no compensatory LV enlargement, so the forward ejection fraction (EF) is reduced, leading to low CO.

Long-standing severe mitral regurgitation

- There is enlargement of the LA, which accommodates the volume overload with minimal rise in LA pressure.
- The LV dilates, and large stroke volume (SV) compensates for regurgitation, maintaining the forward expelled volume.
- LV failure (LVF) results from long-standing volume overload.
- The low-pressure regurgitant pathway masks LVF—EF often normal, even when the LV function is very impaired.

Clinical features

- *Acute severe MR:* pulmonary oedema (common), hypotension, cardiogenic shock. This is a medical emergency (see ➔ Acute mitral regurgitation post-MI, p. 83).

History

- Chronic MR is initially asymptomatic.
- Reduced CO, resulting in fatigue, dyspnoea, and orthopnoea.
- Palpitations (↑ SV/associated AF). Systemic embolization (less common than in MS).
- Features of right HF in later stages.
- Symptoms/risk factors of endocarditis or IHD.

Physical examination

- Rapid upstroke in arterial pulse. Irregularly irregular pulse in AF. Prominent ‘a’ waves in JVP in patients in SR. Large ‘v’ waves if associated TR. Forceful apex displaced laterally (LV dilatation). Apical systolic thrill.

Auscultation

- Pansystolic murmur loudest at the apex and radiating into the axilla. Soft first heart sound. Loud MV closure sound helpful in excluding severe MR. Wide splitting of S_2 due to premature aortic valve closure. Prominent low-pitched S_3. A mid-diastolic flow murmur may follow S_3, even in the absence of MS.

Mitral regurgitation: investigations

- *ECG:* LA enlargement, LVH, RA enlargement in PHT. AF common in chronic MR.
- *CXR:* cardiomegaly, LA and LV enlargement, and pulmonary venous congestion. Calcified mitral annulus may be seen.
- *TTE:* demonstrates MV anatomy (lesion and type of MR). Colour Doppler to detect MR. Assessment of LV function from EF, end-systolic dimension and end-diastolic dimension (NB in compensated MR, EF is always misleading (overestimated) because of the low-resistance retrograde pathway).
- *TOE:* shows anatomy in greater detail and allows assessment of valve repair feasibility. Should be performed pre-/intraoperatively.
- *Cardiac catheterization:* not always required. Ventriculography can quantify MR severity and EF. Detection of coexisting valve lesions and CAD.

Classification of organic mitral regurgitation

(See Table 4.5)

Table 4.5 Classification of mitral regurgitation

	Mild	Moderate	Severe
Qualitative			
MV morphology	Normal/abnormal	Normal/abnormal	Flail leaflet/ruptured papillary muscle
Colour flow MR jet	Small, central	Intermediate	Large central jet or eccentric jet reaching posterior wall of LA
Flow convergence zone	None or small	Intermediate	Large
CW signal of MR jet	Faint/parabolic	Dense/parabolic	Dense/triangular
Semi-quantitative			
VC width (mm)	<3	Intermediate	≥7
Pulmonary vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal
Mitral inflow	A-wave dominant	Variable	E-wave dominant
Quantitative			
EROA (mm^2)	<20	20–39	≥40
R Vol (mL)	<30	30–59	≥60

MV, mitral valve; MR, mitral regurgitation; LA, left atrium; CW, continuous wave; VC, vena contracta; EROA, effective regurgitant orifice area; R Vol, regurgitant volume.

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Prognosis

Prognosis depends upon the aetiology of MR; for example, ischaemic MR confers significantly worse prognosis. Outcome is poor in symptomatic severe MR—33% survival at 8 years without surgical intervention. Death occurs mostly from HF, but there is a substantial incidence of sudden death, which may be arrhythmia-related.

Mitral regurgitation: management

Medical management

- Although at ↑ risk of endocarditis, the 2015 ESC guidelines for management of infective endocarditis do not recommend routine prophylaxis for MR.
- Asymptomatic patients with mild MR are managed conservatively with serial echocardiography.
- Asymptomatic patients with chronic severe MR, normal LV function, and no PHT or AF can be managed conservatively with serial echocardiography.
- In acute MR, nitrates and diuretics can reduce filling pressures. In chronic MR, there is no evidence to support the use of vasodilators. However, ACEis and β-blockers should be considered when HF has developed.
- In AF, rate control and anticoagulation—warfarin (target INR 2–3) or DOACs may be suitable (NB new-onset AF is a class IIa indication for surgery in chronic severe MR).

Monitoring

- Regular monitoring is required in MR due to the potential for deterioration over time (see Box 4.8).
- Should be undertaken in all patients with more than trace MR who do not yet meet the criteria for surgical intervention.

Box 4.8 Monitoring intervals for mitral regurgitation

- *Mild MR:* if normal LV size and function, every 3–5 years
- *Moderate MR:* annual clinical review and TTE every 1–2 years
- *Severe MR:* if LVEF >60%, TTE and clinical review every 6 months

Surgical treatment

- Should be considered in patients with severe MR.
- *Indicated for symptomatic patients and any of the following:*
  - LVEF >30% (ESC Class I recommendation).
  - LVEF ≤30%, symptoms are refractory to medical therapy, and a durable valve repair is likely (ESC Class IIa recommendation).
- *Asymptomatic patients with severe MR may need surgery if there is:*
  - Worsening of LV function: LVEF ≤60% or LV end-systolic dimension ≥45mm (ESC Class I recommendation).
  - New AF (ESC Class IIa recommendation).
  - PHT (ESC Class IIa recommendation).
- *MV repair is strongly preferred to valve replacement* (see Box 4.9)—it is the only intervention that restores life expectancy to normal and offers event-free survival that is superior to medical management or replacement (ESC Class I recommendation).

- Likelihood of repair is highly dependent on surgeon expertise.
- Repair minimizes the risk of haemorrhage and thromboembolism, reoperation, LV dysfunction, and endocarditis.
- Multi-segment prolapse and heavily calcified valves are more difficult to repair than single-segment prolapse and non-calcified valves.
- Percutaneous MV repair methods (edge-to-edge mitral clip and coronary sinus annuloplasty band) are currently being tested but are not yet approved.
- *Risk of surgery:* 1–2% mortality and stroke in 65-year-old patient with no other major morbidity and good LV function. Ischaemic MR and endocarditis risk rises to around 2–5%.

Box 4.9 Unfavourable features on transthoracic echocardiography for mitral valve repair

- *MV deformation:* coaptation distance ≥1cm, tenting area >2.5–3cm^2, complex jets originating centrally and posteromedially, posterolateral angle >45°.
- *Local LV remodelling:* interpapillary muscle distance >20mm, posterior papillary–fibrosa distance >40mm, lateral wall motion abnormality.
- *Global LV remodelling:* EDD >65mm, ESD >51mm.

EDD, end-diastolic diameter; ESD, end-systolic diameter.

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Mitral valve prolapse

Definition

- Mitral valve prolapse (MVP) is systolic billowing of one or both MV leaflets above the plane of the MV annulus into the LA.

Epidemiology

- Prevalence is 1–2.5%. More common in men than in women.

Aetiology

- The most common cause is myxomatous degeneration.
- Occurs in ↑ frequency in patients with connective tissue disorders, including Marfan's syndrome, Ehlers–Danlos syndrome, pseudoxanthoma elasticum, and osteogenesis imperfecta.
- Present in 20% of ostium secundum ASDs.
- Several chromosomal loci have been linked with familial MVP.

Pathophysiology

- Myxomatous degeneration and excess mucopolysaccharides lead to thickened, enlarged valve leaflets in one or more segments.
- Prolapse due to elongated chordae tendinae and excess leaflet tissue.
- MV leaflet (usually posterior—P2 segment) prolapses into the LA during ventricular systole.

Clinical features

History features

- Mostly asymptomatic.
- Atypical chest pain (potentially related to autonomic dysfunction).
- Palpitations resulting from ventricular/supraventricular arrhythmias.
- Symptoms of MR if prolapse significant.

Examination findings

- Mid- or late systolic click due to tensing of the chordae tendinae and prolapse of the leaflet.
- Late systolic murmur due to associated MR.
- Feature suggesting an underlying connective tissue disorder (e.g. tall status, hypermobility, and large arm span in Marfan's syndrome; see ➲ Connective tissue disorders: Marfan's syndrome, pp. 454–5).

Investigations

- *ECG:* usually normal. Some non-specific changes may be seen.
- *CXR:* normal if there is no significant MR.
- *TTE:* systolic displacement of one or both MV leaflets by >2 mm into the LA beyond the high points of the mitral annulus. Should also assess the degree of MR.

Management

- Infective endocarditis prophylaxis no longer recommended (see ➲ Endocarditis prophylaxis—non-dental, p. 337).
- β-blocker for chest pain and palpitations.
- Anticoagulation if in AF or prior thromboembolic event.
- Management as for MR (see ➲ Mitral regurgitation: management, pp. 204–5).

Aortic stenosis: overview

Epidemiology

- Most common valve lesion in the UK.
- ♂ > ♀ and ↑ with age.
- Two per cent of people aged >65 years have echocardiographic features of AS.
- Congenital bicuspid AS presents ~20 years earlier.
- Becoming more common (ageing population, improved diagnosis).

Causes

- *Acquired:* degenerative calcific AS (most common); rheumatic fever, Paget's disease of bone, end-stage renal failure, ochronosis.
- *Congenital:* bicuspid aortic valve, 1–2% of live births. Bicuspid aortic valve results in chronic turbulent flow, which leads to calcification and fibrosis of leaflets with reduced valve area.

Pathogenesis

- AS can occur at the level of the valve, or above (supravalvular) or below (subvalvular) the aortic valve.
- Degenerative AS results from years of normal stress on the valve.
- Similar risk factors as for IHD (↑ BP, ↑ lipids, DM).
- Inflammation occurs within the valve; Ca^{2+} is deposited along flexion lines, causing immobility and reduced excursion and opening area.
- Rheumatic AS is due to adhesion and fusion of commissures, with fibrosis and retraction.

Pathophysiology

- Progressive narrowing of the valve orifice results in compensatory LVH to maintain SV.
- LVH results in a stiff, non-compliant ventricle, with elevated end-diastolic pressure (diminished coronary perfusion pressure).
- The atrial component of LV filling then becomes more significant.
- Pressure overload eventually results in LVF and ↓ transvalvular gradient because of ↓ SV through the valve.

Clinical features

History

- *Classical triad:* angina, syncope, dyspnoea.
- *Angina pectoris:* from ↑ oxygen demand due to LVH and ↑ wall tension (↓ subendocardial perfusion). Occurs in two-thirds of cases—only half of these have obstructive coronary lesions.
- *Syncope:* on exertion, cannot ↑ CO in the setting of peripheral vasodilatation, leading to ↓ cerebral perfusion.
- *Dyspnoea:* pulmonary oedema causing dyspnoea (worsened by AF).
- *Other features:*
    - Sudden death: from ventricular arrhythmias.
    - Bleeding: acquired von Willebrand (vW) disease and platelet dysfunction due to shearing of vW factor multimers and platelets (Heyde's syndrome).

Physical examination

- *Pulse:* slow-rising, small-volume pulse (pulsus parvus et tardus)—best felt at the carotid.
- *BP:* narrow pulse pressure, in advanced AS, SBP is ↓.
- *JVP:* prominent 'a' wave.
- Sustained, heaving apical impulse. If CCF develops, the apex beat is displaced inferolaterally.
- *Thrill:* systolic thrill is felt in the aortic area (second intercostal space on the right) during full expiration.

Auscultation

- *S_1:* normal or soft.
- *S_2:* in mild AS, S_2 is normal (i.e. A_2 precedes P_2). In moderate AS, S_2 becomes single (closure of the aortic valve is delayed until it coincides with closure of the pulmonary valve (PV)). In severe AS, there is paradoxical splitting, with A_2 after P_2. S_2 may be obscured by the murmur of AS if severe.
- *Other sounds:* S_4 is often heard (atrial contraction into stiff ventricle) and systolic ejection click (if valve pliable).
- *Murmur:* mid-systolic crescendo–decrescendo ejection murmur is heard throughout the precordium, but best heard at the right upper sternal border in full expiration. Radiates to the carotids. As AS severity worsens, the murmur peaks later and extends later through systole.

Prognosis

Rate of progression is highly variable, although the valve area is estimated to decrease ~0.1cm^2 per year. Symptoms are often not present until AS is severe (gradient across valve often >100mmHg). Once symptoms occur, prognosis significantly worsens without surgical intervention.

- Patients who present with angina have a 5-year median survival.
- Patients who present with syncope have a 3-year median survival.
- Patients who present with dyspnoea due to CHF have a 2-year median survival.

Bicuspid aortic valve

- *Prevalence:* 1–2%; ♂ > ♀.
- *Form:* bicuspid valve normally forms with fusion of two cusps to form a ridge (raphe). Location of this fusion contributes to variable presentation/morphology; >70% result from fusion of left and right coronary cusps.
- *Aortopathy:* significant association with ascending aorta dilatation (25% risk of requiring aortic surgery) and coarctation of the aorta.
- *Post-aortic valve replacement (AVR) follow-up:* due to potential for aortic dilatation, follow-up should continue regularly post-AVR. If aorta ≥45mm, then annual follow-up required (ESC Class I recommendation).
- *Familial screening:* bicuspid aortic valve has a strong familial association. Screening of first-degree relatives may be considered (ESC Class IIa recommendation). No data to support effectiveness.

Aortic stenosis: investigations

- *ECG:* LVH with strain, LBBB, LA enlargement.
- *CXR:* calcification in the valve or root, post-stenotic dilatation in the ascending aorta.
- *TTE:* calcified valve with restricted opening (M-mode). Colour Doppler to detect concomitant AR. CW Doppler to assess velocity/gradient across the valve (see ➔ TTE: Doppler, pp. 490–1). Determine the valve area and EF. Assessment of valve morphology (bicuspid vs tricuspid) and ascending aorta dilatation.
- *Cardiac catheterization:* to assess for concomitant CAD prior to valve surgery (present in 50% with calcific AS). Pullback gradient across the valve not assessed (significant risk of embolic events with this—CW Doppler sufficiently accurate).
- *Dobutamine stress echocardiography (DSE):* consider in patients with low-gradient severe AS to detect myocardial reserve and differentiate true stenosis from pseudo-stenosis (see Table 4.7).

Classification

- AS severity is defined by jet velocity through the valve, mean pressure gradient, and valve area (continuity equation) (see Table 4.6).
- AS severity can be complex when the criteria outlined do not agree.
- *High-gradient AS:* this occurs when the jet velocity/mean gradient suggest severe AS (see Table 4.6). This can result from high transvalvular flow/CO (see Box 4.10). If reversible causes of high CO are excluded, this should be considered severe AS.
- *Low-gradient AS*: this occurs when the valve area is <1cm^2, but the mean gradient/jet velocity are not severe. Review echocardiographic images to ensure quality and measurements are correct. Should prompt consideration of two additional factors: flow (i.e. SV index (SVi)) and EF:
  - *Normal flow (SVi >35mL/m^2):* severe AS is unlikely.
  - *Low flow (SVi ≤35mL/m^2) and LVEF <50%:* undertake low-dose DSE. This will help to distinguish severe from pseudo-severe AS.
  - *Low flow (SVi ≤35mL/m^2) and LVEF ≥50%:* establishing true severe AS difficult. Table 4.8 details factors that ↑ the likelihood of severe AS. Cardiac CT to assess valve calcification.

Table 4.6 Classification of aortic stenosis

Severity	Jet velocity (m/s)	Mean gradient (mmHg)	Valve area (cm^2)
Mild AS	<3	<20	>1.5
Moderate AS	3–4	20–40	1–1.5
Severe AS	>4	>40	<1

Box 4.10 Causes of high transvalvular gradients

Non-reversible	*Reversible*
Aortic regurgitation	Fever
Atrioventricular shunts	Anaemia
	Hyperthyroidism

Table 4.7 Severe vs pseudo-severe aortic stenosis in low-gradient setting

	Severe	Pseudo-severe	No flow reserve
Definition	Severe AS leading to LV systolic dysfunction, preventing sufficient transvalvular gradients	Moderate AS with small valve area due to low flow across valve (from another cause of LV dysfunction), preventing full valve opening	SV is at maximum, no ↑ in DSE, so unable to differentiate severe from pseudo-severe
Stroke volume with DSE	↑	↑	No change
Valve area with DSE	No change	↑	No change
Mean gradient with DSE	↑	No change	No change
Next steps	Manage as severe	Monitor as moderate	Cardiac CT

AS, aortic stenosis; DSE, dobutamine stress echocardiography; LV, left ventricular; SV stroke volume.

Table 4.8 Features associated with ↑ likelihood of severe aortic stenosis in low-flow, low-gradient normal left ventricular ejection fraction

Clinical criteria	Typical symptoms Elderly patient (aged >70 years)
Qualitative data	LV hypertrophyReduced LV longitudinal function
Quantitative data	Mean gradient 30–40mmHg AVA ≤0.8cm^2 Low flow confirmed by other techniques (e.g. TOE, CMR) Calcium score by cardiac CT: severe AS likely ≥2000 (men) or ≥1200 (women)

LV, left ventricular; AVA, aortic valve area; TOE, transoesophageal echocardiography; CMR, cardiac magnetic resonance; CT, computed tomography; AS, aortic stenosis.

Source: data from Baumgartner H *et al*. *Eur Heart J*. 2017;**18**(3):254–75.

Aortic stenosis: management

Medical management

- No medical treatments are proven to prevent or delay the disease process in the valve leaflets. No benefit of statins (SEAS trial).
- There is no effective medical treatment to improve prognosis:
  - β-blockers ↓ cardiac oxygen demand and may ↑ coronary blood flow.
  - Drugs reducing afterload (e.g. ACEis) were contraindicated due to the potential to worsen coronary blood flow. However, several trials (e.g. RIAS) have shown a benefit from ACEis in moderate/severe AS in ↓ LVH and improving symptoms.
  - *Nitrates contraindicated:* theoretical risk of ↓ BP in severe AS.
  - Severe AS with HF in patients unsuitable for intervention should be treated as per HF guidelines.

Monitoring

- *Mild AS without calcification:* follow-up with TTE every 2–3 years.
- *Moderate/mild AS with calcification:* TTE every year.
- *Severe AS:* clinical review and TTE every 6 months.
- *Bicuspid aortic valve:* if no aortic dilatation or significant stenosis, then TTE every 3–5 years; otherwise annual imaging is required.

Indications for intervention

- Intervention is indicated in patients with symptoms (see ➔ Clinical features, pp. 208–9) and severe high-gradient AS (ESC Class I recommendation).
- Indicated in patients with symptomatic severe low-flow, low-gradient AS with LVEF <50% once pseudo-severe AS has been excluded (ESC Class I recommendation).
- Should be considered in symptomatic severe low-flow, low-gradient AS with normal EF. However, confirmation is needed that AS is severe (ESC Class IIa recommendation).

Patients with asymptomatic aortic stenosis

- Should have exercise testing if physically active, to elicit symptoms.
- If symptoms on exercise testing or risk factors (peak velocity >5.5m/s, severe calcification, progression ≥0.3m/s per year, elevated neurohormones, or severe PHT), the patient should be considered for intervention (ESC Class IIa recommendation).

Transcatheter aortic valve replacement

- Bioprosthetic valves mounted on expandable stents are placed in the aortic position via the transfemoral or transapical route.
- Once positioned, the valve is expanded by using a balloon.
- Transcatheter aortic valve implantation (TAVI) has been shown to be superior to medical therapy in patients not suitable for open valve replacement (PARTNER B trial). In patients at high surgical risk (e.g. EuroSCORE 18–29%), there are similar (PARTNER) or improved rates of survival vs open repair.

- When compared with low-risk surgical patients, TAVI is associated with lower composite risk of death, stroke, and rehospitalization at 1 year (PARTNER 3).
- Current guidelines suggest TAVI should be considered for patients at high or intermediate risk (ESC and American Heart Association (AHA)/American College of Cardiology (ACC) guidelines). However, indications in low-risk patients are likely to be added in the future.

Surgical treatment

- Surgery is currently recommended as the treatment of choice for symptomatic AS in patients with low surgical risk.
- Acute decompensation of severe AS is a medical emergency.
- AVR is reasonable for asymptomatic moderate or severe AS when undergoing concomitant CABG, aortic, or valve surgery.
- AVR is generally a safe procedure. General risks are detailed in Table 4.9. High-volume centres have ↓ mortality/morbidity rates.
- Bioprosthetic valves are preferred in older patients. They have excellent freedom from valve degeneration. May be used in younger patients who want to avoid the 2–4% annual risk of stroke.

Table 4.9 Risks of aortic valve replacement

	AVR only (%)	AVR + CABG (%)
In-hospital mortality	2.3	4.1
1-year mortality	6.8	10.6
Stroke	1.2	1.9
Pacemaker implantation	4.4	3.6

AVR, aortic valve replacement; CABG, coronary artery bypass graft.

Source: data from: Holzhey D, *et al*. Current results of surgical aortic valve replacements: insights from the German aortic valve registry. *Ann Thorac Surg*. 2016;**101**(2): 658–66.

Balloon aortic valvuloplasty

- Introduced as non-surgical alternative treatment for AS.
- Prognosis same as for medical management because of procedural complications (~3% mortality and ~6% MI/severe AR/myocardial perforation) and restenosis rates (50% restenosis in 3–6 months).
- Limited indications for balloon aortic valvuloplasty:
  - Bridge to TAVI/surgical AVR in haemodynamically unstable patients with severe AS or in those with severe AS who require urgent major non-cardiac surgery (ESC Class IIb recommendation).
  - Diagnostic procedure in patients with severe AS and potential alternate cause for symptoms (ESC Class IIb recommendation).
  - In patients with severe myocardial dysfunction, prerenal insufficiency, or other organ dysfunction that may reverse with balloon aortic valvuloplasty. Only in centres that can escalate to TAVI (ESC Class IIb recommendation).

Aortic regurgitation: overview

Causes

- *Valvular:* RHD (often combined with AS/MS/MR), infective endocarditis, degenerative calcific (with AS), bicuspid aortic valve, trauma.
- *Aortic root disease:* hypertension, aortic dissection, Marfan's syndrome. Other causes are rare: osteogenesis imperfecta, syphilitic aortitis, spondyloarthritides (ankylosing spondylitis, Reiter's syndrome, etc.), arteritis (Takayasu's, giant cell).

Incidence

- Less common than AS (accounts for 11% of valve disease).
- Valvular causes are becoming less frequent and aortic root causes now account for >50% of cases.
- Of valvular causes, 50% are due to degenerative disease.

Pathogenesis

- *Valvular disease:* valvular fibrosis and fusion of cusps result in retraction of cusps, such that they cannot coapt properly.
- *Subacute bacterial endocarditis (SBE):* direct destruction of valve cusps/vegetations.
- *Aortic root disease:* progressive dilatation of the aortic root causes failure of coaptation of cusps and regurgitation.

Pathophysiology

- As the valve fails, ↑ % of SV regurgitates into the LV.
- CO is maintained by compensatory LV dilatation and LVH, ↑ SV, but at the expense of ↑ end-diastolic volume.
- Volume overload leads to eccentric hypertrophy; myocyte function deteriorates, and further LV dilatation occurs, leading to LV decompensation.

Clinical features

Acute aortic regurgitation

- *Symptoms:* dyspnoea is common (↑ forward CO in the setting of non-compliant LV (LVEDP) leads to pulmonary oedema).
- *Signs:* hypotension and cardiogenic shock.
- Acute AR is a medical emergency (see ➔ Acute heart failure, pp. 836–7).

History

- *Asymptomatic:* in chronic AR, LVEDP is low due to LV dilatation.
- *Dyspnoea:* chronic volume overload leads to LVF and chronic HF.
- *Chest pain:* due to angina or importantly aortic dissection (e.g. chest pain radiating to the back).
- Ask about symptoms of endocarditis.

Physical examination

- *Wide pulse pressure:* collapsing (water-hammer) pulse, a large number of associated eponymous signs (see Table 4.10).
- *Apex beat:* displaced inferolaterally and diffuse/hyperdynamic. May feel apical systolic thrill.

Table 4.10 Eponymous signs of severe aortic regurgitation

Corrigan's	Visible carotid pulsation
De Musset's	Head nodding with each pulse
Müller's	Visible pulsation of the uvula
Traube's	Pistol shot femorals. Loud bruit heard with stethoscope over femoral artery
Quincke's	Visible capillary pulsation in nail bed
Duroziez's	Systolic and diastolic bruits heard over femoral artery when artery is compressed

Auscultation

- *A_2:* may be normal (or louder) if AR is due to aortic root pathology, and may be soft or absent if AR is due to aortic valve pathology.
- *Other sounds:* S_3 may be heard with dilated LV or with incipient failure.
- *Murmur:* murmur of AR is a high-pitched, early diastolic decrescendo murmur immediately following A_2. Best heard with patient sitting up and leaning forward in expiration. Heard most clearly along the left upper sternal border (occasionally along the right sternal border if the aortic root is dilated). Duration of murmur in diastole correlates with severity of AR.

Table 4.11 Other murmurs in aortic regurgitation

Ejection systolic	Similar to AS, may be audible (as a result of either mixed AR/AS or turbulent flow due to ↑ stroke volume)
Austin Flint	A mid-diastolic murmur heard at the apex due to antegrade flow across MV orifice, which has been narrowed by a combination of rising LV pressure and jet of AR directed at the anterior MV leaflet

AS, aortic stenosis; AR, aortic regurgitation; MV, mitral valve; LV, left ventricular.

Aortic regurgitation: investigations

- *ECG:* LVH with strain, left axis deviation.
- *CXR:* in chronic AR, there is an enlarged cardiac shadow. Dilated ascending aorta with aortic root pathology.
- *TTE:* colour Doppler and CW Doppler confirm diagnosis and assess severity. M-mode measures the aortic root and LV dimensions, and EF. Assessment of valve morphology and aortic root dilatation.
- *Cardiac MRI:* quantifies regurgitation fraction when TTE measurements are equivocal.
- *Cardiac CT:* gated CT to assess maximum aortic sinus to commissure diameter (measured at end diastole).
- *Cardiac catheterization:* to assess for concomitant CAD prior to valve/root surgery. Consider aortography in left anterior oblique (LAO) projection to show the aortic root and AR severity.

Classification

Table 4.12 shows the classification of AR.

Table 4.12 Classification of aortic regurgitation

	Mild	Moderate	Severe
Qualitative			
Valve morphology	Normal or abnormal		Abnormal/flail or large defect
AR jet			
Colour flow width	Small	Intermediate	Large (if central)
CW signal	Incomplete	Dense	Dense
Diastolic flow reversal			
Descending aorta	Brief	Intermediate	Pan-diastolic
Abdominal aorta	Absent	Absent	Present
Semi-quantitative			
VC width (mm)	<3	3–6	≥6
Pressure half-time (ms)	>500	200–500	<200
Quantitative			
EROA (mm^2)	<10	Mild to moderate: 10–19 Moderate to severe: 20–29	≥30
R Vol (mL)	<30	Mild to moderate: 30–44 Moderate to severe: 45–59	≥60

AR, aortic regurgitation; CW, continuous wave; VC, vena contracta.; EROA, effective regurgitant orifice area; R Vol, regurgitant volume.

Source: data from Lancellotti P *et al*. *Eur Heart J*. 2013;**14**(7):611–44.

Prognosis

- Chronic AR can be well tolerated for many years and is associated with a good prognosis.
- 5-year survival ~75%, 10-year survival ~50%.
- Prognosis worsens as symptoms develop (see Box 4.11).
- Acute severe AR, however, is associated with high mortality from LVF, and early intervention is indicated.

Box 4.11 Natural history of aortic regurgitation

Asymptomatic patients with normal LV function

- Progression to symptoms/signs of CCF: <6%/year
- Progression to asymptomatic LV dysfunction: <3.5%/year
- Sudden death: <0.2%/year

Asymptomatic patients with LV systolic dysfunction

- Progression to cardiac symptoms: >25%/year

Symptomatic patients

- Mortality rate: >10%/year

LV, left ventricular; CCF, congestive cardiac failure.

Aortic regurgitation: management

Monitoring

- *Asymptomatic mild/moderate AR with normal LV:* routine follow-up (every 1–2 years) with TTE.
- *Asymptomatic severe AR with normal LV:* frequent (6-monthly) follow-up; sooner if symptoms occur. In uncertain cases, check BNP/NT-proBNP; ↑ associated with LV function deterioration.
- *Aorta:* if the ascending aorta is dilated (>40mm), undertake CT/CMR. Should be followed up with measurements during TTE valve follow-up. An ↑ of >3mm should be validated by CT/CMR.

Medical management

- Aims to reduce symptoms in patients with severe AR.
- *Severe AR with LV dysfunction or symptoms:* symptoms of CCF respond to loop diuretics and digoxin, while arrangements are made for surgery. Vasodilators (ACEis, CCBs) reduce afterload (thus reducing regurgitation), offer good symptomatic relief, and may improve the haemodynamic profile.
- *Anginal chest pain:* can be treated with nitrates (lower afterload), but use β-blockers with caution (see below).
- *Hypertension:* can worsen AR; therefore, treat in the usual manner.
- *Acute severe AR:* urgent intervention recommended. Nitroprusside (to ↓ afterload) and inotropic agents (dopamine, dobutamine) ↑ CO and ↓ LVEDP, and are useful to manage the patient temporarily before surgery. IABP is contraindicated.
- *β-blockers:* prevent compensatory tachycardia and prolong the diastolic phase, allowing for the regurgitant fraction to ↑. Generally avoided, and if used, should be done with significant caution.

Indications for intervention

- *Ascending aorta:* dilatation of the aorta above thresholds (see Table 4.13) should prompt consideration of intervention (ESC Class IIa recommendation). If there is aortic valve disease, then valve repair is recommended at the time of surgery (in patients with a tricuspid aortic valve—ESC Class I recommendation).
- *Symptoms:* symptomatic patients should undergo AVR (ESC Class I recommendation).
- *LV systolic function:* AVR is indicated in patients with LVEF ≤50%, even if asymptomatic (ESC Class I recommendation).
- *Concomitant cardiac surgery:* should have valvular intervention on the aortic valve if the patient is undergoing CABG, or surgery on the ascending aorta/another valve (ESC Class I recommendation).
- *Severe LV dilatation:* if LV end-diastolic diameter >70mm or end-systolic diameter >50mm (or end-diastolic diameter >25mm/m^2), should consider valvular intervention (ESC Class IIa recommendation).
- *Asymptomatic AR:* if LV function is normal, these patients do not require intervention and should have serial follow-up.

Table 4.13 Ascending aorta dilatation thresholds for intervention

Conditions	Threshold (mm)
Marfan's syndrome + risk factors*	≥45
TGFBR1 or *TGFBR2* mutations (including Loeys–Dietz syndrome)	≥45
Bicuspid aortic valve with additional risk factors*/ coarctation	≥50
Marfan's syndrome without additional risk factors	≥50
All other patients	≥55

* Family history of aortic dissection, past history of vascular dissection, severe aortic regurgitation/mitral regurgitation, desire for pregnancy, hypertension, ↑ aortic size >3mm/year (by using the same imaging technique).

Surgical intervention

- AVR is the standard procedure for most patients requiring intervention for AR. AVR is a safe, effective procedure.
- Aortic root replacement, with or without preservation of the native aortic valve, is required in patients with ascending aorta dilatation.
- Choice of bioprosthetic or mechanical valve replacement is dependent on a number of factors (see Table 4.14 for further details).
- Valve-sparing procedures may be useful in young patients with normal leaflets where aortic intervention is due to aortic root dilatation—durability may be better than bioprosthetic valves.

Table 4.14 Bioprosthetic vs mechanical valves in aortic position

Category	Recommendation	Strength
Anticoagulation	Bioprosthetic: where good-quality anticoagulation is unlikely or contraindicated due to bleeding risk	I
Thrombus	Bioprosthetic: if reoperating for mechanical valve thrombosis despite good anticoagulation	I
Valve deterioration	Mechanical: in patients at high risk of valve deterioration (age <40 years, hyperparathyroidism)	I
Patient age	Mechanical: patients aged <60 years	IIa
	Bioprosthetic: patients aged >65 years	IIa
Pregnancy	Bioprosthetic: should be considered in young women contemplating pregnancy	IIa
Risk of redo surgery	Mechanical: should be considered in patients with high risk of redo valve surgery	IIa

Source: data from Vahanian *et al*. *Eur Heart J*. 2022;**43**(7):561–632.

Tricuspid stenosis

Causes

- RHD (almost always associated with MS), congenital, carcinoid, pacemaker lead. Extremely rare.

Clinical features

- *History:* fatigue, anorexia, peripheral oedema.
- *Physical examination:* wasting, oedema, hepatomegaly, ↑ JVP, prominent 'a' waves.
- *Auscultation:* rumbling mid-diastolic murmur at left lower sternal edge in inspiration.

Investigations

- *ECG:* SR with signs of RA enlargement (↑ 'P' waves in leads II and V1—often coincides with signs of LA enlargement because of MS), but no RVH.
- *CXR:* enlarged RA, but normal PA size.
- *TTE:* two-dimensional image can show thickened, restricted leaflets. CW Doppler is diagnostic. Severe tricuspid stenosis (TS)—valve area $<1.0\text{cm}^2$. Look for coexisting MS.

Management

- Salt restriction and diuretics are the mainstay of medical therapy.
- Tricuspid valve repair or replacement depends on valvular morphology and surgical experience. Bioprosthetic valves give better results than mechanical valves. There is evidence of usefulness of tricuspid valve balloon valvuloplasty, but use remains controversial.
- *Left-sided valve surgery:* if coexisting left-sided disease is being operated on, then tricuspid intervention should be undertaken (ESC Class I recommendation).
- *Symptomatic:* patients with symptoms and severe TS should be operated on (ESC Class I recommendation).

Tricuspid regurgitation

Causes

- *Functional or secondary TR:* normal leaflets with RV annular dilatation is common; due to MV disease, PHT, or congenital heart disease (common).
- *Primary TR:* endocarditis most common (particularly IV drug abuse), transvalvular pacing wires, Marfan's syndrome, Ebstein's anomaly, RHD, carcinoid.

Clinical features

- *History:* usually minimal. Late features are leg swelling (oedema); ascites leading to nausea, anorexia, and abdominal swelling; and abdominal pain (tender, congested liver).
- *Physical examination:* cachexia/wasting, jaundice, oedema, AF, elevated JVP with systolic CV waves, tender and pulsatile hepatomegaly.
- *Auscultation:* RV S_3 often heard (↑ in inspiration), presystolic murmur (PSM) audible at left sternal edge (LSE) (↑ in inspiration). Murmur loudest in TR secondary to PHT.

Investigations

- *ECG:* non-specific, may show evidence of underlying condition.
- *CXR:* cardiomegaly in patients with functional TR, occasionally distended azygos vein, pleural effusion.
- *TTE:* colour Doppler confirms diagnosis. CW Doppler of TR jet can assess PA systolic pressure. Two-dimensional images can give an idea of the cause of TR (RV infarction, VSD, Ebstein's, etc.). Severe TR: jet width >0.7cm and systolic flow reversal in hepatic veins.

Management

- In the absence of PHT, TR is generally well tolerated and may not require specific treatment (indeed, in SBE of the tricuspid valve, valve excision is sometimes performed, with good recovery).
- RV failure symptoms respond to diuretics and fluid/salt restriction.
- Valve repair preferred. Annuloplasty ring is management for secondary TR.

Primary tricuspid regurgitation

- *Severe TR:* tricuspid valve repair should be undertaken in patients with symptoms (ESC Class I recommendation), progressive RV dilatation (ESC Class IIa recommendation), or need for left-sided valve surgery (ESC Class I recommendation).
- *Moderate TR:* repair should be considered in those undergoing left-sided valve surgery (ESC Class IIa recommendation).

Secondary tricuspid regurgitation

- *Severe TR:* should be undertaken if undergoing left-sided surgery. (ESC Class I recommendation) or if develops progressive RV dilatation despite left-sided surgery without ongoing left-sided valve dysfunction (ESC Class IIa recommendation).
- *Mild/moderate TR:* should be considered if tricuspid valve annulus >40mm (or >21mm/m^2) and undergoing left-sided valve surgery (ESC Class IIa recommendation).

Pulmonary stenosis

Causes

- Congenital (virtually all, e.g. Noonan's syndrome), carcinoid, rheumatic, compression.

Clinical features

- *History:* usually none. If long-standing severe stenosis—exertional dyspnoea, light-headedness/syncope (inability to ↑ CO). Ultimately may develop TR symptoms or RV failure (see previous).
- *Physical examination:* prominent 'a' wave in JVP, RV heave, occasionally thrill in second left intercostal space.
- *Auscultation:* widely split S_2 (as PV closure becomes later), P_2 becomes softer (unless stenosis is supravalvular), ejection systolic murmur (ESM) at left edge of upper sternum—heard best in inspiration.

Investigations

- *ECG:* RVH and RA enlargement.
- *CXR:* dilated PAs, occasionally with calcification of valve, if severe—then oligaemic lung fields.
- *TTE:* confirms diagnosis and can show level of stenosis (valvular, supravalvular, or RVOT) and severity. Severe pulmonary stenosis (PS): jet velocity >4m/s or max. gradient >60mmHg. Will also show associated conditions (ASD, patent ductus arteriosus (PDA), Fallot's, etc.).
- *Cardiac catheterization:* to assess severity of obstruction and haemodynamic effects.

Management

- In general, invasive intervention is recommended when the gradient across the valve is >40mmHg at rest or when symptoms occur.
- *Medical:* supportive/symptomatic treatment of RV failure, diuretics, fluid restriction (cautious).
- *Balloon valvuloplasty:* treatment of choice for stenosis at valvular level. Highly effective and safe, with good long-term results. PR is common following valvuloplasty, but is rarely clinically important.
- *Surgical:* valvotomy is very effective, with minimal recurrence. *PV replacement* is indicated if not suitable for above treatments or for severe PR following these treatments.

Pulmonary regurgitation

Causes

Any cause of PHT (causes dilatation of valve ring), infective endocarditis, connective tissue disease (e.g. Marfan's syndrome), iatrogenic (following valvotomy or PA catheter placement), carcinoid, after surgery for congenital heart disease (e.g. repair of tetralogy of Fallot).

Clinical features

- *History:* often asymptomatic. Symptoms occur when PHT or RV failure exists. Then patients develop dyspnoea on exertion, lethargy, peripheral oedema, and abdominal pain.
- *Physical examination:* RV heave, occasionally a thrill in pulmonary area.
- *Auscultation:* P_2 may be delayed (large SV), loud (if ↑ pulmonary BP) or soft (if PV stenosis). Murmur of PR heard best in third/fourth intercostal space on the left adjacent to the sternum, ↑ during inspiration.

Investigations

- *ECG:* RVH (if ↑ pulmonary BP), RBBB/rsR pattern in lead V1.
- *CXR:* enlarged PA and RV.
- *TTE:* two-dimensional images may show RV dilatation/hypertrophy. Abnormal septal motion if RV volume overload. PR seen on colour Doppler and quantified with pulsed Doppler. Severe PR—colour jet fills outflow tract.

Management

- Usually supportive treatment suffices.
- Treat RV failure in usual way (diuretics, etc.).
- If PR is due to PV ring dilatation secondary to PHT, treating the underlying cause of PHT can ↓ severity of PR (e.g. MV surgery).
- If there is symptomatic right HF with severe PR, then PV replacement (PVR) should be considered. Indications for PVR in asymptomatic individuals remain unclear.

Prosthetic heart valves

Types

- *Mechanical:* bileaflet (St Jude Medical®, Carbomedics®) most common today. Ball-and-cage (Starr–Edwards®) or tilting disc (Medtronic Hall®) (see Fig. 4.3).
- *Bioprosthetic:* porcine (stented or stentless) or bovine pericardium (Carpentier–Edwards).
- *Non-prosthetic valves:* homograft (preserved cadaveric human valve), autograft (PV—Ross procedure).

Mechanical valves

- Minimal risk of structural failure. Lifetime risk of reoperation for non-structural valve dysfunction is ~5%.
- Thrombogenic—therefore requiring lifelong warfarin therapy.
- Even with optimal INR (see Table 4.15), there is 2–4% linearized annual lifetime risk of major thromboembolic or haemorrhagic events, including stroke.

Table 4.15 Target INR for mechanical prosthesis

Prosthesis thrombogenicity	Example valves	Patient factors[*]	
		None	≥1
Low	Carbomedics, Medronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical, On-X, Sorin Bicarbon	2.5	3.0
Medium	Other bileaflet valves with insufficient data	3.0	3.5
High	Lillehei-Kaster, Omniscience, Starr–Edwards, Björk–Shiley, other tilting discs	3.5	4.0

[*] Mitral or tricuspid valve replacement, previous thromboembolism, atrial fibrillation, mitral stenosis, left ventricular ejection fraction <35%.

Source: data from Baumgartner H *et al. Eur Heart J*. 2017;**38**(36):2739–91.

Mechanical valves and invasive procedures

- Management of patients undergoing PCI is covered in ➔ CCS: management of antiplatelets and anticoagulation, pp. 52–3.
- Anticoagulation should be continued for minor surgical procedures.
- If major surgery is required, anticoagulation should be stopped and heparin (LMWH or UFH) used to bridge.
- Timing depends on patient characteristics and thrombotic risk.

Tissue valves

- Bioprosthetic or homograft.
- Do not require anticoagulation but are not as durable as mechanical valves (15-year failure rate of 5–20% for bioprostheses, depending on patient age—best durability in older patients).

- Linearized annular risk of thromboembolism of 0.5%.
- More likely to have postoperative gradient than mechanical valves in smaller sizes.

Valve haemodynamics

- Different prostheses have unique profiles/effective orifice area (EOA).
- For any given valve dimension, bioprosthetic valves have the smallest EOA, and bileaflet valves the best.

Assessment of prosthetic valve function

Clinically

Each prosthetic valve produces a distinctive sound. Dysfunction may be indicated by new sounds, a change in sound or volume of sound, or a new (or changing) murmur.

Imaging modality

- *Fluoroscopy:* assess mechanical valve leaflet movement. ↓ motion in thrombosis, excessive movement of base ring if valve dehisced.
- *TTE:* limited use because of shadow caused by metal in valve. Can be used to look at valve ring motion (in mechanical valves), leaflet motion (in tissue valves), and regurgitation (with Doppler).
- *TOE:* better at assessing prosthetic MV function, but less good at prosthetic aortic valve assessment.
- *MRI:* safe in majority of modern mechanical valves. Expensive and time-consuming—therefore, reserved for cases when TTE/TOE are inconclusive.
- *Cardiac catheterization:* Can assess valve gradient and quantify regurgitation. Risk of passing catheter across mechanical valves—therefore, used prior to reoperation or when other tests are inconclusive.

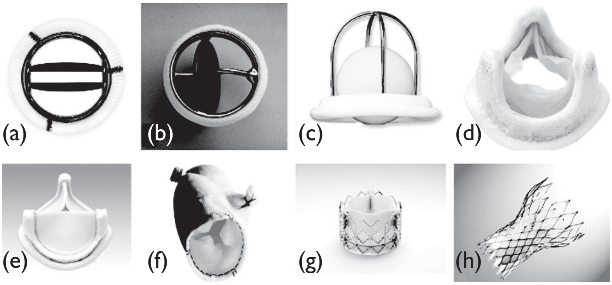

Fig. 4.3 Common types of heart valve prostheses. (a) Bileaflet mechanical valve (St Jude). (b) Monoleaflet mechanical valve (Medtronic Hall). (c) Caged ball valve (Starr–Edwards). (d) Stented porcine bioprosthesis (Medtronic Mosaic). (e) Stented pericardial bioprosthesis (Carpentier–Edwards Magna). (f) Stentless porcine bioprosthesis (Medtronic Freestyle). (g) Percutaneous bioprosthesis expanded over a balloon (Edwards Sapien). (h) Self-expandable percutaneous bioprosthesis (CoreValve).

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Prosthetic valve complications

Valve thrombosis

- *Epidemiology:* 0.1–5.7% per patient-year; <0.01% per day if anticoagulation withheld (may be necessary for life-threatening bleed).
- *Risks:* inadequate anticoagulation and mitral/tricuspid prostheses. Bileaflet valve can continue to work partially, but single leaflet/tilting disc may fail catastrophically.
- *Clinical presentation:* pulmonary oedema, embolization/stroke, sudden death, ↓ intensity of valve sounds,
- *Investigation:* ↓ movement of leaflets on TTE or fluoroscopy (and ↑ valve gradient on TTE). CT suggesting distal embolism.
- *Treatment:*
    - *Mechanical:* urgent valve replacement recommended for valve thrombosis without significant comorbidity (ESC Class I recommendation). Thrombolysis should be considered if surgery not available/very high risk or for non-obstructive thrombus >10mm (ESC Class IIa recommendation). Anticoagulation with heparin may be sufficient if thrombus is <5 mm. High recurrence rate if valve not replaced.
    - *Bioprosthetic:* anticoagulation with warfarin or UFH (ESC Class I recommendation).
- *Prognosis:* valve replacement for valve thrombus has a mortality rate of <15%; thrombolysis has a mortality rate of <10% (with embolization in <20%). Thrombolysis may be more effective for aortic valve thrombosis and in recent (<2 week) onset.

Embolization

- *Epidemiology:* in non-anticoagulated patients, ~5% per patient-year (causing death/stroke), 1–2% per patient-year if on therapeutic anticoagulation. Most manifest as cerebral infarctions.
- *Risks:* AF, age >70 years, ↓ LV function, mitral prostheses, ball-and-cage valves, >1 valve. Consider endocarditis in patients with prosthetic valves presenting with peripheral embolization. If cerebral embolization, perform immediate CT to exclude bleed (if bleed confirmed, withhold anticoagulation and seek specialist help).
- *Treatment:* treat underlying risk factors; optimize anticoagulation. Low-dose aspirin (75mg od) can be added after consideration of the risk–benefit ratio.

Haemolysis

- *Epidemiology:* a low level of background haemolysis is common in patients with mechanical prostheses (even when functioning normally). Severe haemolysis is uncommon and usually secondary to valve dysfunction (leakage, dehiscence, infection).
- *Investigations:* ↓ Hb, ↑ LDH, ↓ serum haptoglobin level, reticulocytosis.
- *Treatment:* treat underlying problem (including further valve surgery), blood transfusion, folic acid, ferrous sulfate. Occasionally re-replacement is required for cases requiring frequent blood transfusion.

Endocarditis

(See ➔ Prosthetic valve endocarditis, pp. 330–1.)

- *Epidemiology*: lifetime risk of around 1–6% of patients with prosthetic valves. Early endocarditis cases occur within 60 days of valve surgery (<1%), and late endocarditis occurs >60 days since surgery.
- *Aetiology:* early prosthetic valve endocarditis (PVE) usually arises from skin/wound infections or from indwelling IV cannulae. Commonly due to *Staphylococcus aureus*, *Staphylococcus epidermidis*, Gram-negative bacteria, and fungi. Late PVE has similar organisms to native valve endocarditis (mainly streptococci). Similar risk for tissue and mechanical valves.

Structural valve degeneration and reoperation

- *Epidemiology:* structural valve degeneration (SVD) is inevitable for all currently available bioprosthetic valves if the patient lives long enough. Valves calcify and leaflets tear, resulting in regurgitation (40%), stenosis (30%), or both (40%).
    - *Aortic valve:* freedom from SVD >85% at 10 years. Degeneration ↑ rapidly beyond 15 years of follow-up.
    - *TAVI:* data limited by generally short follow-up (first TAVI in 2004) and highly comorbid population. PARTNER-1A suggests similar rates to surgical valve replacement.
    - *Mitral valve:* ~80% freedom from SVD at 10 years.
    - *Mechanical valves:* freedom from reoperation (for pannus, endocarditis, and thrombosis) for mechanical valves >95% at 10 years and ~90% at 10 years.
- *Definition:*
    - *Stenosis:* ↑ mean gradient ≥10mmHg (possible SVD), or ≥20mmHg (significant SVD) during follow-up with associated ↓ in valve area or abnormal leaflet morphology/mobility.
    - *Regurgitation:* new-onset or worsening transprosthetic regurgitation.
- *Risks:* earlier-generation valves, young age, mitral position, renal failure (because of greater pressure differential across the closed MV in systole, compared with the closed aortic valve in diastole):
    - No clear evidence that porcine > bovine, stented > stentless, homografts > xenografts.
    - Although renal failure predisposes to accelerated calcification, there is no ↑ in reoperation, because of lower life expectancy.
- *Investigations:* clinical and TTE findings of regurgitation or stenosis.
- *Treatment:* as for primary valve lesion, although closer follow-up is required as prosthetic valve function can deteriorate more quickly—reoperation poses 1–5% extra risk of mortality/morbidity above first-time surgery. For aortic valve disease, valve-in-valve TAVI can be considered.

Patient–prosthesis mismatch

Occurs after AVR where the replacement is 'too small' for the patient.

- *Definition:*
    - EOA < than that of a normal human valve.
    - ERO indexed to body surface area (BSA) $<0.85\text{cm}^2/\text{m}^2$ (normal indexed EOA $<2.0 \pm 0.3\text{cm}^2/\text{m}^2$). Moderate mismatch 0.65–$0.85\text{cm}^2/\text{m}^2$; severe mismatch $<0.65\text{cm}^2/\text{m}^2$.

  - There are specific parameters for each valve type which should be consulted. For example, a 21mm Carpentier–Edwards Perimount valve has an EOA of 1.2cm^2 and would provide an indexed EOA of <0.8cm^2/m^2 if inserted into a patient with BSA >1.6m^2.
- *Incidence:*
  - *Severe:* patient–prosthesis mismatch 2–11% of post-operative AVRs.
  - *Moderate:* 20–70% of AVRs.
- *Risks:*
  - Stented valves in smaller sizes are partially stenotic, and mild to moderate transvalvular aortic gradients are not uncommon in the immediate post-operative period.
- *Outcomes:*
  - Patient prosthesis mismatch is associated with ↓ post-operative cardiac index and NYHA functional class, reduced LV mass regression, poorer survival, and late adverse events.

Paravalvular leak

- *Incidence:* 0–1.5% per patient-year.
- *Risks:* St Jude Silzone® valves, thinner sewing rings, calcified annulus, incomplete debridement of calcium/previous sutures, active endocarditis.
- *Outcomes:* late paravalvular leaks are suggestive of prosthetic valve endocarditis. Paravalvular leaks generally result in haemolysis that is more severe than that associated with older, normally functioning prosthetic valves.
- *Investigations:* TTE, endocarditis workup, screen for haemolysis.
- *Treatment:* severe haemolysis, insufficiency, valve dehiscence, and evidence of endocarditis are surgical indications; otherwise frequent TTE follow-up.

Further reading

Habib G, Lancellotti P, Antunes MJ, *et al.;* ESC Scientific Document Group. 2015 ESC guidelines for the management of infective endocarditis. *Eur Heart J*. 2015;**36**:3075–123.

Vahanian A, Beyersdorf F, Praz F, *et al*.; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2022;**43**(7):561–632.

Chapter 5

Heart muscle diseases

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Classification

- The ESC Working Group on Myocardial and Pericardial Diseases groups heart muscle disorders according to morphology.
- A cardiomyopathy is defined as 'a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of CAD, hypertension, valvular heart disease (VHD) and congenital disease sufficient to cause the observed myocardial abnormality'.[1]
- Cardiomyopathies are divided into several phenotypes and subdivided into familial (more than one family member affected) and non-familial forms (no other family members affected). The latter is further subdivided into idiopathic and acquired disorders (Fig. 5.1).
- Table 5.1 illustrates the spectrum of diseases that can give rise to various cardiomyopathies.
- It is important to note that there are limitations to this classification—for example, where several different cardiomyopathies are caused by the same mutation, if multiple mutations cause a single cardiomyopathy, if phenotypes overlap, or if one phenotype develops into another.

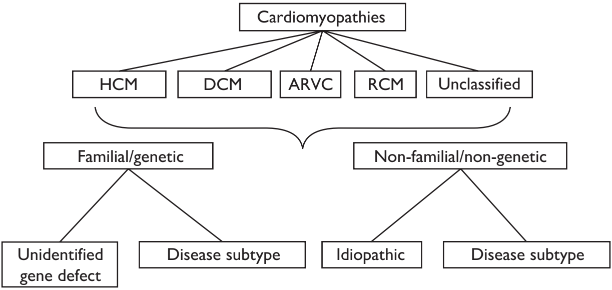

Cardiomyopathies
HCM
DCM
ARVC
RCM
Unclassified
Familial/genetic
Non-familial/non-genetic
Unidentified gene defect
Disease subtype
Idiopathic
Disease subtype

Fig. 5.1 Classification of cardiomyopathies.

Reproduced from Elliott P *et al*. *Eur Heart J*. 2008;**29**(2):270–6, with permission from the ESC. Copyright © The European Society of Cardiology 2008.

Table 5.1 Causes of cardiomyopathies

	Familial	Non-familial
HCM	• Unknown gene • Mutations in sarcomeric genes • Neuromuscular disease (e.g. Friedreich's ataxia) • Mitochondrial disease • Storage disorders (e.g. Anderson–Fabry, Pompe, PRKAG2, Danon) • Syndromes (e.g. Noonan syndrome, LEOPARD syndrome)	• Amyloid • Drug-induced (e.g. steroids) • Autoimmune
ACM	• Unknown gene • Mutations in desmosomal proteins	
DCM	• Genetic mutations	• Idiopathic • Myocarditis • Infections • Endocrine • Drugs • Nutritional • Pregnancy • Alcohol • Rate-related cardiomyopathy
RCM	• Genetic mutations • Familial amyloidosis • Haemochromatosis	• Amyloidosis • Scleroderma • Endomyocardial fibrosis • Carcinoid • Radiation • Drugs

HCM, hypertrophic cardiomyopathy; ACM, arrhythmogenic cardiomyopathy; DCM, dilated cardiomyopathy; RCM, restrictive cardiomyopathy.

Reference

1. Elliott PM, Andersson B, Arbustini E, *et al*. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology working group on myocardial and pericardial disease. *Eur Heart J*. 2008;**29**:27.

Dilated cardiomyopathy: overview

Definition

- Dilated cardiomyopathy (DCM) is characterized by the 'presence of LV or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions (hypertension/valve disease) or coronary disease sufficient to cause global systolic impairment'.[1]

Epidemiology

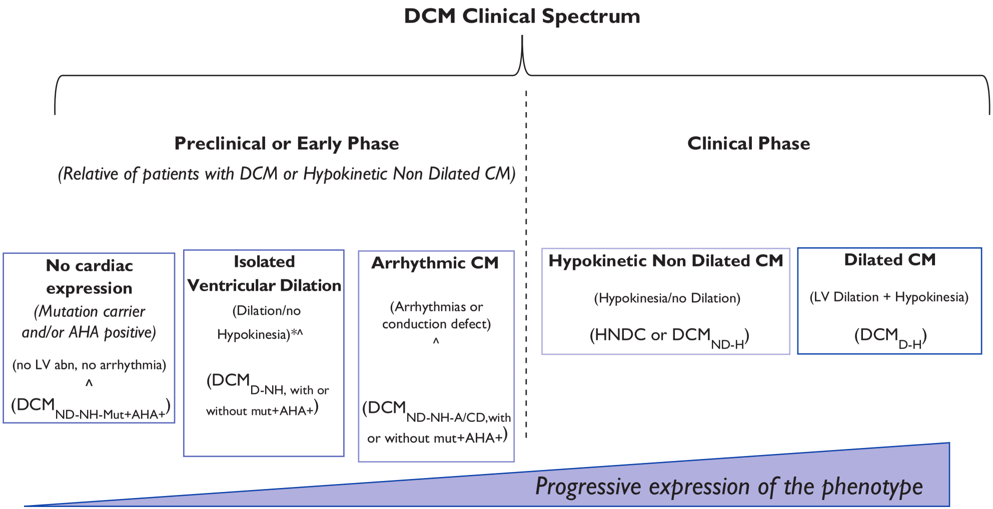
- The prevalence of DCM is around 1 in 2500.

Classification

- Patients with DCM have a variable clinical course. The revised definition of the stages of DCM[1] (see Fig. 5.2) has divided the DCM clinical spectrum into a preclinical and a clinical phase.

Reference

1. Pinto YM, Elliott PM, Arbustini E, *et al*. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2016;**37**:1850–8.


DCM Clinical Spectrum
Preclinical or Early Phase
(Relative of patients with DCM or Hypokinetic Non Dilated CM)
Clinical Phase
No cardiac expression
(Mutation carrier and/or AHA positive)
(no LV abn, no arrhythmia)
^
(DCM$_{ND-NH-Mut+AHA+}$)
Isolated Ventricular Dilation
(Dilation/no Hypokinesia)*^
(DCM$_{D-NH, with or without mut+AHA+}$)
Arrhythmic CM
(Arrhythmias or conduction defect)
^
(DCM$_{ND-NH-A/CD, with or without mut+AHA+}$)
Hypokinetic Non Dilated CM
(Hypokinesia/no Dilation)
(HNDC or DCM$_{ND-H}$)
Dilated CM
(LV Dilation + Hypokinesia)
(DCM$_{D-H}$)
Progressive expression of the phenotype

*Shown by two independent imaging modalities, ^mutation carrier or not; anti-heart autoantibody (AHA) positive or negative

Fig. 5.2 The disease spectrum of DCM. ** Hypokinetic non-dilated cardiomyopathy (left ventricular ejection fraction <45%) 'not explained by abnormal loading conditions or coronary artery disease'.

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DCM: aetiology

Genetics

To date, over 50 disease-related genes have been identified. A causative mutation is found in around 25% of individuals, and most are inherited in an autosomal dominant (AD) fashion. The most commonly affected gene is titin (*TTN*), accounting for ~25% of familial DCM cases. Importantly, these mutations may occur in 2% of the population. Therefore, development of DCM may be due to oligogenic inheritance, modifiers, or environmental factors. The next most common gene affected is lamin A/C (*LMNA*, 6%), followed by sarcomeric genes (e.g. β-myosin heavy chain (*MYH7*, 4%).

Neuromuscular disorders

Neuromuscular disorders include myotonic dystrophy (MD), and Duchenne (DMD) and Becker muscular dystrophy (BMD) (see ➔ Muscular dystrophies, pp. 274–5).

Infection

- Viral: adenovirus, Coxsackie virus, echovirus, influenza A and B, hepatitis C, parvovirus B19, CMV, EBV, human herpesvirus (HHV), HIV, VZV.
- Bacterial: *Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Haemophilus influenzae*, *Mycobacterium*, *Corynebacterium diphtheriae*, typhoid.
- Spirochaetal: *Borrelia burgdorferi* (Lyme disease), *Leptospira* (Weil disease), syphilis.
- Rickettsial: *Coxiella burnetii* (Q fever), *Rickettsia rickettsii* (Rocky Mountain spotted fever).
- Fungal: *Aspergillus*, *Candida*, *Cryptococcus*.
- Protozoal: *Trypanosoma cruzi*, *Toxoplasma gondii*.

Autoimmune disorders

- Giant cell myocarditis, inflammatory DCM (biopsy-proven non-infectious myocarditis), systemic lupus erythematosus (SLE), rheumatoid arthritis, scleroderma, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, sarcoidosis, polymyositis/dermatomyositis (see ➔ Chapter 10).

Endocrine disorders

- Hypo-/hyperthyroidism, phaeochromocytoma, Cushing's/Addison's disease, acromegaly.

Toxins and overload

- Drugs (chemotherapeutic agents, chronic cocaine use) and alcohol. Iron overload secondary to haemochromatosis/repeated blood transfusion.

Nutritional deficiency

- Selenium, thiamine (beriberi) (See ➔ Nutritional deficiency and cardiac effects, pp. 282–3).

Other

- Takotsubo cardiomyopathy, peripartum cardiomyopathy, tachycardiomyopathy (HR <100bpm, recovery of LV function within 4 weeks) (see ➔ Takotsubo cardiomyopathy, p. 276; ➔ Peripartum cardiomyopathy, p. 418).

DCM: clinical features and differential diagnosis

Clinical features

Symptoms

- Chest pain, shortness of breath, reduced exercise tolerance, paroxysmal nocturnal dyspnoea (PND), orthopnoea, oedema, fatigue, palpitations, dizziness, loss of consciousness.

Signs

- Raised JVP, laterally displaced apex, peripheral oedema, crepitations/ reduced air entry, hepatomegaly, ascites.

Differential diagnosis

Ischaemic cardiomyopathy

- Evidence of ≥75% stenosis in the left main stem/proximal left anterior descending artery/≥2 arteries, or evidence of subendocardial/ transmural scar on MRI.

Hypertensive cardiomyopathy

- Prolonged history of uncontrolled hypertension, as well as ↑ wall thickness/mass.

Burnt-out hypertrophic cardiomyopathy

- History of HCM, with areas of ↑ LV wall thickness with extensive LGE on MRI (see ➔ Hypertrophic cardiomyopathy, p. 240).

Arrhythmogenic cardiomyopathy

- Arrhythmogenic right ventricular cardiomyopathy (ARVC) predominantly affects the RV. However, arrhythmogenic left ventricular cardiomyopathy (ALVC) is much more difficult to differentiate from DCM. This may also be further complicated by the finding of desmosomal gene mutations in both conditions (see ➔ Arrhythmogenic cardiomyopathy: overview p. 250).

Left ventricular non-compaction

- Left ventricular non-compaction (LVNC) may be difficult to distinguish from DCM, as prominent trabeculation is not uncommon in the latter (see ➔ Left ventricular non-compaction: overview pp. 258–9).

Athlete's heart

- An athlete is more likely to be asymptomatic, with normal BNP/NT-proBNP levels, normal ECG (as per international recommendations), normal diastolic indices, high peak VO_2 on exercise testing, LVEF ↑ by >11% on exercise testing, and reversibility of remodeling on deconditioning (see ➔ The athlete's heart: left ventricular structural changes, pp. 870–1).

DCM: investigations

DCM screening blood tests

A comprehensive set of blood tests for DCM is included in Box 5.1.

Box 5.1 Dilated cardiomyopathy screen

- FBC
- U&Es (renal failure secondary to heart failure/underlying pathology)
- LFTs, GGT (liver involvement secondary to heart failure/underlying pathology, e.g. alcohol)
- TFTs (hyper-/hypothyroidism)
- Ferritin/transferrin saturation (haemochromatosis)
- NT-proBNP
- CK (myopathies)
- ESR (infection/autoimmune)
- CRP (infection/autoimmune)
- ANA/ANCA/ENA/RF (autoimmune)
- ACE (sarcoid)
- Thiamine/selenium—if dietary insufficiency suspected
- Serology is generally unhelpful due to the high background seropositivity rates; however, individuals should be tested for HIV, and where there has been recent travel/high suspicion Lyme/typhoid/protozoa/fungi.

FBC, full blood count; U&Es, urea and electrolytes; LFTs, liver function tests; GGT, γ-glutamyl transferase; TFTs, thyroid function tests; NT-proBNP, N-terminal proB-type natriuretic peptide; CK, creatinine kinase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibodies; ANCA, anti-cytoplasmic antibodies; ENA, anti-extractable nuclear antibody; RF, rheumatoid factor; ACE, angiotensin-converting enzyme.

All individuals should have the following investigations

- *Urine:* proteinuria, urinary metanephrines, toxicology if indicated.
- *ECG:* may demonstrate ischaemia, arrhythmias, conduction abnormalities (*LMNA*-positive individuals, neuromuscular disorders, Lyme disease, sarcoidosis), voltage criteria for chamber enlargement.
- *CXR:* assessment for pulmonary congestion (upper lobe venous diversion, interstitial oedema, pleural effusions, and Kerley B lines), cardiomegaly, and hilar lymphadenopathy in sarcoidosis.
- *Echocardiography:*
  - Identifies chamber dilatation
  - Provides highly accurate assessment of volumes and function
  - Accurate assessment of diastolic function
  - Strain analysis may offer an opportunity for evaluation of early effects on LV systolic function in the preclinical phase
  - Identifies valvular abnormalities such as functional MR
  - Identifies dyssynchrony
  - Inferolateral regional wall abnormalities are often seen in acute myocarditis and muscular dystrophy
  - Demonstrates complications of DCM such as intramural thrombus

  - Aids in diagnosis of alternative causes of HF such as hypertensive heart disease, previous MI, VHD, pericardial disease, and intracardiac shunts.
- *Exercise testing:* with or without measurement of maximum ventilatory oxygen consumption by using CPET; useful to assess for arrhythmias and functional capacity.
- *Holter monitoring:* useful to evaluate tachycardiomyopathy and to detect non-sustained VT (NSVT)/VT resulting from scar tissue.
- *MRI:* provides the goal standard for assessment of volumes, function, and tissue characterization, as well as superior assessment of the RV. T2 mapping and short tau inversion recovery (STIR) imaging may identify oedema suggestive of acute inflammation. Myocardial fibrosis occurs in one-third of patients with DCM. Newer imaging techniques, such as T1 mapping, may enable differentiation between diseased and healthy myocardium.
- *CTCA/coronary angiography:* CAD should be excluded in individuals aged ≥35 years and those aged <35 years if suspected high risk of CAD.

May be required

- *CT-PET:* if sarcoid or myocarditis suspected. Careful dietary preparation is required to optimize the use of this technique.
- *Endomyocardial biopsy (EMB):* enables tissue diagnosis in myocarditis, giant cell myocarditis (multinucleated giant cells), eosinophilic myocarditis, and sarcoidosis, and can help to determine if inflammation is due to viral persistence or an autoimmune process.
- *Genetic analysis:* can identify a cause for familial disease and guide family screening. It can also be helpful in differentiating some causes of cardiomyopathy (e.g. arrhythmogenic cardiomyopathy (ACM)).
- *Muscle biopsy/electromyography (EMG):* if a neuromuscular aetiology is suspected.

DCM: management and prognosis

Prognosis

- One-third of individuals will experience recovery after 3 months of OMT. Some forms of DCM may be completely reversed. This is commonly seen in alcohol-related cardiomyopathy (following a period of abstinence), peripartum cardiomyopathy, and acute inflammatory cardiomyopathy.

Management

Symptoms

- Management of DCM focuses on relieving symptoms and improving prognosis and quality of life. Pulmonary and peripheral congestion are effectively treated with diuretics.

Prognostic medications

- Prognostically important pharmaceutical therapies inhibit the maladaptive neurohormonal process involving the sympathetic system and renin–angiotensin–aldosterone axis. The acute management of HF is discussed in ➔ Management of acute heart failure, pp. 108–11. Chronic management of HF is discussed in ➔ Pharmacological management in chronic heart failure, p. 102.
- Management of arrhythmias is discussed in ➔ Chapter 3.

Device implantation

- An ICD is recommended when a patient is symptomatic with LVEF <35% despite OMT. Patients with a widened QRS complex may also be a candidate for CRT (CRTD/CRT pacemaker (CRTP)) (see ➔ Device therapy for heart failure, p. 112).
- Interestingly, a recent randomized trial (DANISH) suggested that there was no difference in death rates in those with non-ischaemic cardiomyopathy who received an ICD compared with those who did not; however, a survival benefit may be conferred in younger patients (<68 years of age).

Immunosuppression

- Immunosuppression therapy should be considered in biopsy-confirmed inflammatory DCM and in certain autoimmune and rheumatological diseases (e.g. SLE).

Transplantation

- Cardiac transplantation is discussed in more detail in ➔ Mechanical circulatory support, p. 116; Heart transplantation: indications and work up, p. 120.

Follow-up

- Individuals should be followed up annually (to 2-yearly if stable) with an ECG, echocardiography, Holter monitoring, and exercise testing.

Family screening

- A full family history of at least three generations should be recorded.
- All first-degree relatives of an affected individuals must be screened with an ECG and echocardiography (± Holter monitoring, depending on the predominant phenotype in the affected individual).
- Screening should commence at around the age of 10 years (however, earlier testing may be appropriate in families with early-onset disease) and continue every 2–5 years until the age of 50–60 years, as some forms of DCM may present later in life.

Genetic testing

- Genetic counselling should be performed by trained professionals. This ensures that patients understand the psychological, social, professional, ethical, and legal consequences of a genetic diagnosis.
- This also ensures that information can be gathered around autopsy reports, as well as history from other family members, which assists in establishing the likelihood of a genetic condition and provides more information about the pattern of inheritance.
- Consider genetic testing if two or more family members are affected, the proband is <50 years, or there is a family history of SCD (age <50 years).
- Enables cascade testing of family members who, if they do not have the causative gene, no longer need to be followed up.
- Gene carriers should be surveyed annually to 3-yearly.
- Although generally genetic testing does not offer prognostic information, the exception is if an individual is positive for a mutation in *LMNA*, as well as in other genes (e.g. filamin C (*FLNC*), RNA binding motif protein 20 (*RBM20*), phospholamban). These are associated with conduction disease, ventricular arrhythmias, and SCD. Therefore, early implantation of ICD should be considered.

Hypertrophic cardiomyopathy: overview

Definition

- HCM is characterized by LVH that is not solely explained by loading conditions.[1]

Epidemiology

- HCM affects 1 in 500 individuals.

Basic pathology

- This is characterized by LVH, which usually affects the interventricular septum in an asymmetrical fashion; however, almost any pattern of LVH is possible.
- Histologically, there is evidence of myocyte disarray and myocardial scarring.
- Pathophysiological changes are illustrated in Box 5.2.

Box 5.2 Pathophysiological features of hypertrophic cardiomyopathy

- Systolic function appears to be hyperdynamic as a result of a relative small LV cavity size.
- LV outflow tract obstruction (LVOTO) is caused by the forward motion of the anterior mitral valve leaflet towards the hypertrophied proximal interventricular septum in systole known as systolic anterior motion. There are two main postulated mechanisms, which include: (1) anterior displacement of the papillary muscles; and (2) the Venturi effect, created by rapid ejection of blood across a narrow LV outflow tract, which 'sucks' the anterior mitral valve leaflet against the septum.
- Impaired myocardial relaxation and raised filling pressures.
- Myocardial ischaemia occurs secondary to microvascular dysfunction and wall stress, as well as LVOTO.
- Propensity to potentially fatal supraventricular tachycardia and ventricular tachycardia/fibrillation.
- Systolic function can worsen; eventually the LV dilates and LV wall thickness ↓, leading to a drop in cardiac output and ejection fraction, the so-called 'burnt-out' phase.
- Diastolic function may worsen, leading to severe atrial dilatation and a resultant 'restrictive phenotype'.
- In advanced stages, mitral and tricuspid regurgitation, as well as pulmonary hypertension, may also be present.

Reference

1. Elliott PM, Anastasakis A, Borger MA, *et al*. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;**35**:2733–79.

HCM: aetiology

Sarcomeric gene mutations

HCM is inherited in an AD fashion in 60% of cases. It may be caused by mutations in the genes encoding proteins within the sarcomere. These include myosin-binding protein (*MYBPC3)*, myosin heavy chain (*MYH7)*, troponin T (*TNNT2)*, troponin I (*TNN13*), α-tropomyosin (*TPM1*), and myosin light chain (*MYL3*).

Metabolic

Lysosomal storage disorders (LSDs) (e.g. Danon disease, Pompe disease, Anderson–Fabry disease). LSDs are caused by a deficiency in lysosomal enzymes leading to accumulation of various substrates in cells. Danon disease is an X-linked disorder caused by a defect in the lysosomal-associated membrane protein 2 (*LAMP2*) gene. This presents with skeletal muscle abnormalities, intellectual disability, and cardiac hypertrophy. Pompe disease (glycogen storage disorder II) is an autosomal recessively inherited condition, caused by a deficiency in the lysosomal enzyme acid α-glucosidase. It manifests early in life with failure to thrive, hypotonia, hearing impairment, and cardiac hypertrophy. Without therapy, death may occur in the first year of life. This may also present later in life (10–20 years) with skeletal muscle abnormalities and respiratory pathology. For information about Anderson–Fabry disease, see ➔ Fabry disease, pp. 248–9.

Mitochondrial disorders

- MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) syndrome and MERRF (myoclonic epilepsy with ragged red fibres) syndrome.

Malformation syndromes

- Noonan syndrome is caused by gain-of-function mutations in the Rasopathy (Ras)/mitogen-activated protein kinase (MAPK) signalling pathway. This condition causes stunted growth, facial dysmorphia (wide-spaced eyes, low-set ears, triangular-shaped face, and a webbed neck), mild cognitive delay, pulmonary stenosis, and cardiac hypertrophy.
- LEOPARD syndrome (lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness).

Neuromuscular disorders

Friedreich's ataxia is an autosomal recessive condition caused by expansion of a trinucleotide repeat in the frataxin gene. This can cause ataxia, peripheral neuropathy, diabetes, scoliosis, and cardiac hypertrophy.

Other

- Infiltrative (e.g. amyloid; see ➔ Cardiac amyloidosis: overview, pp. 266–7), endocrine (e.g. phaeochromocytoma, acromegaly), drugs (e.g. anabolic steroids).

HCM: clinical features, differential diagnosis, and investigations

Clinical features

Symptoms

- Patients with HCM are often asymptomatic and identified incidentally during routine medical examination, from an ECG abnormality, or through family screening following diagnosis in a relative.
- *Fatigue and breathlessness:* due to impaired diastolic filling and ↓ CO. Atrial contraction contributes significantly to maintenance of CO, and symptoms typically deteriorate with AF.
- *Chest pain:* may result from myocardial ischaemia.
- *Palpitations, presyncope, and syncope:* may occur due to atrial and ventricular arrhythmias or mechanical obstruction to CO in those patients with LVOT obstruction (LVOTO).
- *HF:* patients may eventually develop severe diastolic dysfunction and/or progressive LV systolic dysfunction, and therefore may present with typical symptoms.
- *Sudden death:* in some cases, may be the initial presentation.
- It is important to ask about symptoms that may lead to a specific diagnosis (e.g. learning disabilities, deafness, visual impairment, neurological symptoms, carpal tunnel, muscle weakness, skin lesions).

Signs

- *Signs of LVH:* a forceful apical impulse and an S_4 heart sound.
- *Outflow tract obstruction:* may cause a double apical impulse and an ejection systolic murmur beginning in mid systole; may be augmented by manoeuvres such as Valsalva or squatting. Pansystolic murmur due to MR as a result of systolic anterior motion (SAM) of the MV.

Diagnosis

- Defined as: wall thickness ≥15mm in one or more LV myocardial segments not explained solely by loading conditions.[1] In first-degree relatives, LVH ≥13mm fulfils the criteria for a diagnosis of HCM.

Differential diagnosis

- *DCM:* in late-phase DCM, there may be LV dilatation/wall thinning.
- *Athlete's heart:* physiological remodelling of the heart in response to exercise may ↑ LV wall thickness and mass. A period of detraining may help to differentiate physiological changes from pathology.
- *Hypertension:* LVH may be caused by ↑ afterload; elderly hypertensive patients may have isolated basal septal hypertrophy. Regression of hypertrophy when started on hypertensives argues against HCM.
- *VHD:* LVH may again be caused by ↑ afterload.

Investigations

- *Bloods:* FBC, U&Es (renal function may be ↓ in amyloidosis), LFTs, TFTs (if amiodarone considered), CK (metabolic, neuromuscular diseases), α-galactosidase A (in men aged >30 years to exclude Fabry disease), serum immunoglobulins and serum/urine electrophoresis (amyloidosis), glucose (may be ↑ in metabolic disorders), BNP or NT-proBNP, troponin, lactate (may be ↑ in metabolic disorders).

Box 5.3 ECG and echocardiographic findings in hypertrophic cardiomyopathy

ECG findings

- Sokolow Lyon criteria for LVH
- ST-segment abnormalities, pathological Q waves, deep TWI
- Ventricular ectopics, NSVT, VT, AF, and SVT
- Pre-excitation (may suggest PRKAG2 syndrome)

Echocardiographic findings

- Asymmetric septal hypertrophy: grossly thickened septum compared with posterior LV wall, with reduced septal motion; however, almost any pattern of LVH is possible. Concentric hypertrophy more common in metabolic and infiltrative disorders
- Small LV cavity with hyperdynamic LV systolic function
- Preserved LV radial function, with reduced longitudinal function
- Impaired diastolic function
- LA enlargement
- SAM ± LVOTO

AF, atrial fibrillation; LA, left atrial; LV, left ventricular; LVH, LV hypertrophy; LVOTO, LV outflow tract obstruction; NSVT, non-sustained ventricular tachycardia; SAM, systolic anterior motion; SVT, supraventricular tachycardia; TWI, T wave inversion; VT, ventricular tachycardia.

- *ECG:* abnormal in >95% of cases. Box 5.3 lists common findings.
- *Echocardiography:* remains the gold standard due to its widespread availability. Echocardiographic features are shown in Box 5.3. TOE should be considered for those undergoing septal myectomy to help guide the procedure.
- *Exercise testing:* helps to assess symptoms, BP response, arrhythmias, ST/T wave changes (note repolarization changes may be exaggerated; if high risk of CAD, further corroboration is required). CPET provides information on gas exchange and exercise limitations. Useful to differentiate HCM from athletic adaptation or metabolic disorders.
- *Holter monitoring:* can provide information on supraventricular and ventricular arrhythmias. In individuals with infrequent palpitations or syncope, an implantable loop recorder (ILR) may be useful.
- *MRI:* helpful to identify apical HCM, evaluate the anterolateral wall, and demonstrate evidence of crypts/myocardial scarring/fibrosis.
- *CTCA/coronary angiography:* it is important to consider CAD in those with typical symptoms and risk factors. The high prevalence of perfusion abnormalities on ischaemia testing makes CTCA more useful under these circumstances. Coronary angiography should be considered in those with typical symptoms of angina and high pre-test probability.
- *EP study:* may be useful to risk-stratify/ablate those with ventricular pre-excitation or to identify and ablate an atrial/ventricular tachyarrhythmia.

Reference

1. Elliott PM, Anastasakis A, Borger MA, *et al*. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;**35**:2733–79.

HCM: management and prognosis

Prognosis

- Mortality in individuals with HCM is around 0.5%/year.

Management

Angina

- Managed with β-blockers, which reduce myocardial oxygen demand and improve diastolic filling. CCBs (verapamil and diltiazem) may be used where β-blockers are not tolerated. Nitrates may be used with caution in those without LVOTO.

Arrhythmias

- β-blockers and amiodarone are the antiarrhythmics of choice in the management of SVT. Ablation may be considered in the case of AF, AFl, or AVRT. VT should be managed with amiodarone (see ➔ Ventricular tachycardia, p. 162). All individuals with AF should be anticoagulated, regardless of their CHA_2DS_2-Vasc score, due to a higher risk of thrombus formation in individuals with HCM.

Heart failure

- Managed as for chronic HF (see ➔ Pharmacological management in chronic heart failure, p. 102).
- Patients with LVOTO may not be able to tolerate high doses of diuretics and vasodilators.
- CRT and transplantation may be considered as necessary (see ➔ Device therapy for heart failure, p. 112; ➔ Mechanical circulatory support, p. 116; Heart transplantation: indications and work up, p. 120).

Left ventricular outflow tract obstruction

- See ➔ Left ventricular outflow tract obstruction, pp. 246–7.

Left ventricular mid-cavity obstruction

- This occurs in around 10% of individuals with HCM. Although this is often managed as for LVOTO, the results may be disappointing.

Sudden cardiac death

- The only effective therapy to prevent SCD is an ICD.

Primary prevention

- A 5-year SCD risk calculation should be performed in all by using the ESC-SCD risk calculator. This is based on a number of clinical variables (see Box 5.4).
- An ICD is indicated in those with a risk score of SCD of >6%. An ICD may be considered in those with a risk score of 4–6% and is usually not indicated if the risk score is <4%.
- This risk score has not been validated in athletes, those aged <16 years, those with metabolic/infiltrative diseases, those whose HCM is part of a syndrome, or post-myectomy/ablation.
- Other variables, such as apical aneurysms/burden of LGE (≥15%) may also affect prognosis; however, their use in a risk score has not yet been validated.

Box 5.4 ESC HCM-SCD risk score variables

- Age
- Family history
- Previous syncope
- Left atrial size
- Maximum left ventricular wall thickness
- Left ventricular outflow tract gradient
- Non-sustained ventricular tachycardia

Secondary prevention

- Secondary prevention ICDs are implanted if the individual has survived a VT/VF arrest and in those who have had symptomatic sustained VTs.

Follow-up

- Individuals should be followed up annually (to 2-yearly if stable) with an ECG, echocardiography, and Holter monitoring. Exercise testing may be performed every 2 years unless otherwise indicated. MRI may be performed every 5 years to assess disease progression.

Family screening

- A full family history of at least three generations should be recorded.
- All first-degree relatives of an affected individual must be screened with an ECG and echocardiography.
- Screening should be considered from the age of 10 years. However, earlier testing may be appropriate in families with early-onset disease. Individuals should be screened annually until the age of 21 years, with further screening performed less frequently (2- to 5-yearly if stable) until the age of 50 years due to the possibility of late development of the phenotype.

Genetic testing

- Consider genetic testing if two or more family members are affected. May be recommended if an individual has a clear HCM phenotype.
- Genetic testing enables cascade testing of family members, who no longer need follow-up if they do not have the causative gene.
- Gene carriers should be surveyed annually to 3-yearly.

Left ventricular outflow tract obstruction

Epidemiology

- Approximately one-third of individuals with HCM have resting SAM. A third have LVOTO on manoeuvres (squatting, Valsalva).
- LVOTO is most likely to occur with hypovolaemia, hypertension, and hypercontractile states.

Aetiology

- It is important to exclude other causes not related to SAM:
  - Subaortic membrane
  - MV leaflet abnormalities
  - Mid-cavity obstruction.

Definition

- LVOTO is defined as ≥30mmHg. It is thought that a gradient of ≥50mmHg is haemodynamically significant.

Clinical features

- Individuals may present with syncope and symptoms after heavy meals or when embarking abruptly on physical activity.

Investigations

- Individuals should undergo two-dimensional echocardiography, with LVOT gradients recorded at rest, on Valsalva manoeuvres, and on standing. If symptomatic, but provoked LVOT gradient is <50mmHg, exercise stress echocardiography is indicated. Dobutamine stress echocardiography is not advised, as it is usually poorly tolerated and is not a physiological test.
- The investigation pathway for LVOTO is shown in Fig. 5.3.

Management

Medical

- Individuals should be counselled on avoiding dehydration, as well as on vasodilators such as nitrates and phosphodiesterase type V inhibitors.
- Medications with positive chronotropic effects, such as digoxin, should also be avoided.
- *β-blockers:* are the first-line management for LVOTO.
- *Non-dihydropyridine CCBs:* may be used if β-blockers are not tolerated. If verapamil is used, care should be taken to monitor the patient if they have severe obstruction (>100mmHg) and also those with PHT, as verapamil may precipitate pulmonary oedema.
- *Disopyramide:* can be added to either β-blockers or CCBs if monotherapy is not sufficient. Disopyramide is a class IA antiarrhythmic. It can cause dry eyes and mouth, as well as urinary retention and constipation. Disopyramide should be used with caution in those with glaucoma or prostatism and if the patient is taking any medications that prolong the QT interval. Due to its effects on QT prolongation, it is important that this is measured prior to, and during, therapy. The dose should be reduced if the QT interval is >480ms.

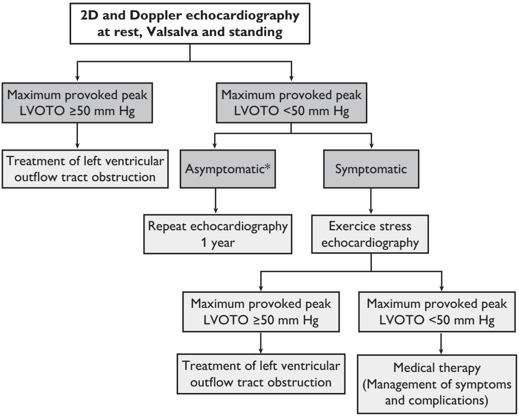
2D and Doppler echocardiography at rest, Valsalva and standing
Maximum provoked peak LVOTO ≥50 mm Hg
Maximum provoked peak LVOTO <50 mm Hg
Treatment of left ventricular outflow tract obstruction
Asymptomatic*
Symptomatic
Repeat echocardiography 1 year
Exercice stress echocardiography
Maximum provoked peak LVOTO ≥50 mm Hg
Maximum provoked peak LVOTO <50 mm Hg
Treatment of left ventricular outflow tract obstruction
Medical therapy (Management of symptoms and complications)

Fig. 5.3 Algorithm for management of left ventricular outflow tract obstruction. *Exercise echocardiography may be considered in individual patients when the presence of a LVOT gradient is relevant to lifestyle advice and decisions on medical treatment.

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- *Diuretics:* although care should be taken, some individuals may also respond to a low-dose diuretic.
- *Acute management:* patients may present with myocardial ischaemia-type symptoms with PHT and oedema. In this situation, IV β-blockers and vasoconstricting agents (phenylephrine) are essential.

Surgical

- Individuals with a gradient >50mmHg and symptoms despite medical therapy may be candidates for surgical intervention.
- *Myectomy:* ventricular septal myectomy (Morrow procedure) involves removing an area of muscle from the basal septum, which extends to below the point of contact of the MV and septum. The main complications include heart block, AR, and VSD. Patients may also undergo simultaneous MV surgery as required.
- *Alcohol septal ablation:* involves injection of alcohol into a septal perforator artery to create an area of scar. The most common complications include heart block and tachyarrhythmias.
- Deciding which procedure is best for the patient is guided by the anatomy and disease phenotype, and should be decided upon at a specialist inherited cardiac condition (ICC) MDT.
- Surgery may be favoured if there is a need for MV intervention, in the presence of significant scar, and in those with severe hypertrophy (<30mm). Both procedures are less effective and pose a greater risk when the patient has mild hypertrophy (<16mm). In these cases, a trial of pacing (short AV interval, also allows ↑ in therapy) or MV intervention may provide better outcomes.
- Both alcohol septal ablation and myectomy should only be performed in recognized centres which specialize in performing these procedures.

Fabry disease

Epidemiology

- The incidence of Fabry disease is around 1 in 40,000.

Aetiology

- Fabry disease is inherited in an X-linked recessive manner.
- Despite the X-linked pattern, women may also exhibit the Fabry disease phenotype, albeit mildly.

Basic pathology

- This is caused by mutations encoding the enzyme α-galactosidase A.
- This enzymatic defect leads to accumulation of globotriaosylceramide in several organs, including the skin, nervous system, kidney, eyes, and heart.

Clinical features

- Clinical manifestations are usually evident by the age of 10 years, with cutaneous angiokeratomata (affecting the hips, groins, and umbilical region), painful neuropathy affecting the hands and feet (acroparaesthesia), hypo-/hyperhidrosis, heat/cold intolerance, corneal deposits, hearing impairment, onset of microalbuminuria, proteinuria, and GI disturbance.
- In the second decade, there may be progression of earlier features, facial dysmorphia, cardiomyopathy, and TIA/CVA.
- By the third decade, there may be progression of earlier features, heart disease (LVH, arrhythmia, angina, dyspnoea), and osteopenia/osteoporosis.
- Cardiac involvement in Fabry disease may take two forms. There may be multiorgan disease, in which cardiac involvement is a feature, but also an atypical variant in which cardiac manifestations occur in isolation.

Investigations

- *Bloods:* measurement of α-galactosidase A levels.
- *ECG:* findings most commonly include LVH. Conduction abnormalities may also be evident.
- *Echocardiography:* abnormalities include the presence of LVH, which can be the earliest and only finding. Atrial enlargement, aortic root dilatation, and valvular thickening (aortic and mitral valves) can also be a feature. The ↑ ventricular wall thickness is due to deposition of globotriaosylceramide within cardiac myocytes. The ↑ wall thickness may mimic HCM, but thickening is generally symmetrical and often concentric. Systolic and diastolic function is often preserved.
- *Holter monitoring:* AF is the most common arrhythmia, followed by VT. Due to lipid deposition throughout the cardiac conduction tissue, any form of heart block can occur and may require PPM implantation.
- *MRI:* may be useful in differentiating other forms of cardiomyopathy, particularly when LVH is the predominant echocardiographic feature. Inferolateral LGE is commonly seen.

- *Coronary angiography:* may be performed if classical anginal symptoms with ischaemic changes on ECG. In the majority of cases, coronary angiography is normal, with ischaemic manifestations due to endothelial dysfunction induced by globotriaosylceramide deposition within coronary arteries.
- *EMB:* diagnosis may be ascertained by EMB. Sarcoplasmic vacuolization is the classic finding on light microscopy of haematoxylin and eosin-stained tissue.

Management

- Enzyme replacement therapy (agalsidase-α and agalsidase-β) has been shown to be effective in ↓ LV mass and improving LV function.
- Management of complications in other organ systems should be provided by the relevant specialist.

Family screening

- Screening should be considered in all first-degree relatives of individuals diagnosed with Fabry disease, and in patients diagnosed with HCM, particularly if LVH is symmetrical and there is no family history of HCM.

Arrhythmogenic cardiomyopathy: overview

Definition

- In 2019, ACM was newly defined as 'a family of diseases that feature structural myocardial abnormalities (identified by macro- and microscopic pathological examination besides cardiac imaging) and ventricular arrhythmias'.[1] This definition includes ARVC and ALVC.
- ACM is a hereditary (and acquired) cardiac disorder, which can affect both the RV and LV concomitantly or in isolation and may progress to ventricular dilatation and failure. Arrhythmias may manifest as frequent ventricular ectopy, NSVT/VT, or cardiac arrest.

Epidemiology

- The prevalence of ACM is between 1 in 2000 and 1 in 5000.

Basic pathology

- Desmosomes are proteins responsible for cellular adhesion and cellular signalling. Abnormal desmosomes in ACM cause disruption of cellular junctions, leading to myocyte detachment and cell death.
- This process may be worsened by physical activity, which results in greater wall stress.
- Fibrofatty tissue, the hallmark of ACM, replaces the damaged tissue. This leads to wall thinning and aneurysmal dilatation. The tissue can also act as a substrate for ventricular arrhythmias through a scar-related re-entry mechanism. The effects on cellular signalling may also ↑ myocardial excitability. Particular sites involved in the RV include the apex and inflow and outflow tracts.
- LV involvement occurs in around 50% of individuals.

Aetiology

- ACM is caused by mutations in genes encoding desmosomes. It is most commonly inherited in an AD fashion; 50% of affected individuals have a family history of ACM.
- Several mutations have been mapped to genes encoding desmosomal proteins (plakoglobin (*JUP*), desmoplakin (*DSP*), plakophilin 2 (*PKP2*), desmocollin 2 (*DSC2*), desmoglein 2 (*DSG2*), transforming growth factor β (*TGF*-β), and transmembrane protein 43 (*TMEM43*).
- The most common gene affected is *PKP2* (in up to 45% of patients).
- An autosomal recessive variant associated with palmoplantar keratosis, wooly hair, and a more malignant clinical course (Naxos disease) has been mapped to the plakoglobin gene on chromosome 17.

Reference

1. Elliott PM, Anastasakis A, Asimaki A, et al. Definition and treatment of arrhythmogenic cardiomyopathy: an updated expert panel report. *Eur J Heart Fail*. 2019;**21**:955–64.

ACM: clinical features and investigations

Clinical features

- Patients are often asymptomatic, but symptoms of palpitations, presyncope, and syncope can occur and may be precipitated by exercise.
- ACM can present at any age in either sex, and the first presentation in healthy young individuals may be exercise-related SCD.
- Other patients present in later life with symptoms of HF with or without ventricular arrhythmias, and advanced cases may be misdiagnosed as DCM.

Investigations

- *ECG and signal-averaged ECG:* T wave inversion (TWI) in RV precordial leads (V1–V3) is common. There may also be epsilon waves, again in leads V1–V3, suggesting delayed ventricular depolarization (see Fig 5.4). In the left dominant form, small-voltage complexes may also be seen. Signal-averaged ECG demonstrates late potentials in individuals with ARVC. Some patients may also demonstrate first-degree AV block or premature AF.

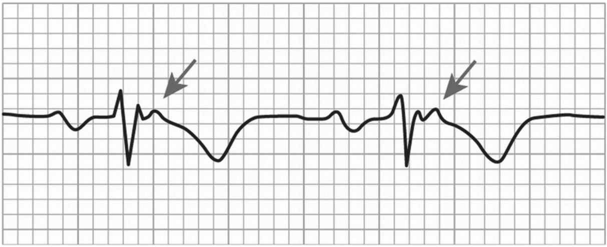


Fig. 5.4 Epsilon wave.

Reproduced from Camm AJ *et al*. *ESC Textbook of Cardiology* (2009), with permission from the ESC. Copyright © The European Society of Cardiology 2009.

- *Echocardiography:* may be normal. Findings can vary from mild focal RV hypokinesia to severe RV dilatation with aneurysm formation and reduced function. LV involvement and biventricular failure may also be seen.
- *Exercise testing:* this may provoke frequent ventricular ectopy and NSVT/VT in patients with ACM.
- *Holter monitoring:* frequent ventricular ectopy and NSVT or sustained VT are recognized features of ACM.
- *MRI:* enables more accurate identification of RV pathology in ARVC; can additionally assess ventricular volumes, global and regional ventricular function, myocardial fat, and LGE (see Fig. 5.5).

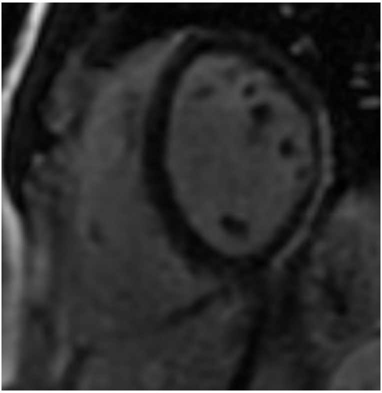


Fig. 5.5 Late gadolinium enhancement in arrhythmogenic left ventricular cardiomyopathy.

- *EP studies:* are useful in differentiating an RV outflow ectopic focus from ARVC. Electro-anatomical mapping may also identify scar tissue.
- *CT-PET:* can also be considered in acute presentations to differentiate ACM from sarcoidosis and to provide a target for EMB.
- *EMB:* tissue diagnosis is problematic, as a transmural sample is necessary. The disease is patchy; therefore, a negative biopsy does not exclude pathology. Furthermore, in the RV, the condition affects the thinnest parts of the RV, ↑ the risk of RV perforation.

ACM: diagnosis

- The current criteria for ARVC[1] considers family history, genetics, and ECG, imaging, and histology parameters (see Table 5.2).
- A diagnosis is based on the presence of two 'major', one 'major' and two 'minor', or four 'minor' criteria from differing categories.
- There are, at present, no equivalent guidelines for ALVC. However, the 2019 consensus statement[2] proposed that the diagnosis of ACM should include arrhythmia (frequent ectopy, VT/NSVT, cardiac arrest), electrical abnormalities (atrial arrhythmias, conduction abnormalities, small voltages on ECG, pattern of LV disease), structural abnormalities, heritability, and exclusion of other phenotypes.

Table 5.2 Task Force criteria for diagnosis of arrhythmogenic right ventricular cardiomyopathy

Global and/or regional dysfunction and structural alterations	MAJOR
	• Echocardiography: regional RV akinesia, dyskinesia, or aneurysm and one of the following (end-diastole):
	  • PLAX RVOT ≥32mm (PLAX/BSA ≥19mm/m^2)
	  • PSAX RVOT ≥36mm (PSAX/BSA ≥21mm/m^2)
	  • *Or* RV FAC ≤33%
	• CMR: regional RV akinesia, dyskinesia, or dyssynchronous RV contraction and one of the following (end-diastole):
	  • RVEDD volume/BSA ≥110mL/m^2 (♂) or ≥100mL/m^2 (♀)
	  • *Or* RVEF ≤40%
	• RV angiography: regional RV akinesia, dyskinesia, or aneurysm
	MINOR
	• Echocardiography: regional RV akinesia or dyskinesia and one of the following (end-diastole):
	  • PLAX RVOT ≥29–31mm (PLAX/BSA ≥16–18mm/m^2)
	  • PSAX RVOT ≥32–35mm (PSAX/BSA ≥18–20mm/m^2)
	  • *Or* RV FAC >33–39%
	• CMR: regional RV akinesia, dyskinesia, or dyssynchronous RV contraction and one of the following (end-diastole):
	  • RVEDD volume/BSA ≥100–109mL/m^2 (♂) or ≥90–99mL/m^2 (♀)
	  • *Or* RVEF >40–44%

Tissue characterization	MAJOR • Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium ≥1 sample, with or without fatty replacement MINOR • Residual myocytes 60–75% by morphometric analysis (or 50–65% if estimated), with fibrous replacement of the RV free wall myocardium ≥1 sample, with or without fatty replacement

Table 5.2 (*Contd.*)

Repolarization abnormalities (>14 years)	MAJOR ● TWI in leads V1–3 or beyond (in the absence of RBBB) MINOR ● TWI in leads V1–2 or V4–6 (in the absence of RBBB) ● TWI in leads V1–4 in the presence of complete RBBB
Depolarization/ conduction abnormalities	MAJOR ● Epsilon wave (reproducible low-amplitude signals between end of QRS complex and onset of T wave in leads V1–3) MINOR ● Signal-averaged ECG with late potentials (if QRS on standard surface ECG <110ms)
Arrhythmias	MAJOR ● Non-sustained or sustained VT of LBBB with superior axis MINOR ● Non-sustained or sustained VT of RVOT configuration, LBBB with inferior axis or unknown, >500 VEs per 24h (Holter monitoring)
Family history	MAJOR ● ARVC in a first-degree relative who meets current Task Force criteria ● ARVC confirmed pathologically from autopsy or surgery in a first-degree relative ● Identification of a pathogenic mutation categorized as associated with ARVC in index patient MINOR ● Suspected ARVC in a first-degree relative ● Premature sudden cardiac death (age <35 years) due to suspected ARVC in a first-degree relative ● ARVC confirmed pathologically or by current Task Force criteria in second-degree relatives

RV, right ventricular; PLAX, parasternal long axis; RVOT, right ventricular outflow tract; BSA, body surface area; FAC, fractional area change; CMR, cardiac magnetic resonance; RVEDD, right ventricular end-diastolic diameter; RVEF, right ventricular ejection fraction; TWI, T wave inversion; RBBB, right bundle branch block; VT, ventricular tachycardia; LBBB, left bundle branch block; ARVC, arrhythmogenic right ventricular cardiomyopathy.

Reproduced from Marcus FI, *et al*. *Circulation* 2010; **121**:1533–41 with permission from Wolters Kluwer Health, Inc. Copyright © 2010 American Heart Association, Inc. 🔗 https://www.ahajournals.org/doi/10.1161/circulationaha.108.840827.

References

1. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;**121**:1533–41.
2. Elliott PM, Anastasakis A, Asimaki A, et al. Definition and treatment of arrhythmogenic cardiomyopathy: an updated expert panel report. *Eur J Heart Fail*. 2019;**21**:955–64.

ACM: management and prognosis

Prognosis

- The estimated mortality is between 0.08% and 3.6% per year.

Management

Lifestyle

- Excessive training or participation in sports should be avoided due to the risk of worsening the condition.

Pharmacological therapy

- β-blockers, specifically sotalol, are recommended as first-line therapy for treatment of frequent ectopy and NSVT.
- Amiodarone may be considered in individuals who are intolerant of β-blockers or in whom β-blockers are contraindicated.
- LVF should be managed as for chronic HF (see ➔ Pharmacological management in chronic heart failure, p. 102).

EPS ± ablation

- Catheter ablation should be considered in those with symptomatic ectopics or ventricular arrhythmias despite medical therapy.

Device implantation

- ICD implantation is indicated in individuals who have survived a cardiac arrest or haemodynamically unstable ventricular arrhythmias. ICDs may also be considered in those who experience haemodynamically stable ventricular arrhythmias.
- An ICC MDT decision should be taken to consider ICD implantation in those who carry specific gene mutations (e.g. *DSP*) or those with LV dysfunction or significant LGE.
- CRT and transplantation may also be considered in these individuals as necessary (See ➔ Device therapy for heart failure, p. 112; ➔ Mechanical circulatory support, p. 116; Heart transplantation: indications and work up, p. 120).

Risk assessment

- There are no clinical risk scores used routinely in clinical practice. However, a recent study has put forward a clinical risk score for the prediction of ventricular arrhythmias and SCD.
- This is based on the following variables: age, sex, recent syncope (past 6 months), NSVT, number of ectopics in 24h, number of leads with TWI, and RVEF.[1]
- Although this shows promise, risk scores such as these require further validation prior to clinical implementation.

Follow-up

- Individuals should be followed up annually (to 2-yearly if stable) with ECG, echocardiography, Holter monitoring, and exercise testing.

Family screening

- A full family history of at least three generations should be recorded.
- All first-degree relatives of an affected individuals must be screened with ECG, signal-averaged ECG, echocardiography, exercise testing, and Holter monitoring.
- Screening should commence at around the age of 10 years (however, earlier testing may be appropriate in families with early-onset disease) and continue every 2–5 years.

Genetic testing

- Predictive genetic testing should be performed where there is significant clinical suspicion or a family history of ACM.
- Genetic testing may be considered in first-degree relatives where there is a borderline diagnosis, but only following MDT discussion.
- It is important to note that negative genetic testing does not exclude the possibility that the cause may be an unknown disease-causing gene.

Reference

1. Cardin-Touringny J, Bosman LP, Nozza A, *et al*. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J*. 2019;**40**:1850–8.1

Left ventricular non-compaction: overview

Definition

- LVNC is characterized by 'prominent trabeculae, deep intertrabecular recesses and a thin compacted layer'.[1] The nomenclature is misleading, as both the RV and LV are commonly involved.
- The disorder is also characterized by systolic and diastolic dysfunction, predilection to arrhythmias, and systemic thromboembolism. There still remains a debate as to whether LVNC is a cardiomyopathy or whether it is part of the phenotype of other cardiomyopathies.

Epidemiology

- The prevalence of LVNC is unknown but is estimated at ~0.014%.

Aetiology

- LVNC may occur as an isolated condition or may be associated with congenital heart disease (CHD), including Ebstein's anomaly, bicuspid aortic valve, and congenital right ventricular outflow tract (RVOT) or LVOT abnormalities such as pulmonary atresia.
- LVNC may be inherited or sporadic, and may demonstrate a greater prevalence in certain ethnic groups such as African Americans.

Inherited

- The genetic basis of LVNC is still unclear but is suggested by a higher prevalence of the condition in first-degree relatives. The inheritance pattern, however, is variable, with AD, X-linked, and even mitochondrial transmission being identified.
- Identified familial cases demonstrate mutations in genes known to cause other cardiomyopathies (HCM, restrictive cardiomyopathies, and DCM) such as *TNNT2*, *MYBPC3*, and *MYH7*.
- Mutations affecting the Notch1 pathway have been implicated in the pathogenesis of LVNC. Moreover, *G4.5* mutations have been identified in Barth syndrome.

Barth syndrome

- This is an X-linked recessive disorder, which results in failure to thrive, stunted growth, and LVNC.
- This is caused by mutations in *G4.5*, which encodes the protein tafazzin which is essential for remodelling of cardiolipin.
- Little is known of the influence of modifier genes or oligogenic effects of genes, as well as of the interaction with environmental factors listed below (see ➲ Sporadic, p. 258).

Sporadic

- LVNC may occur in athletes, pregnant women, and those with sickle cell disease.

Basic pathology

Embryogenic hypothesis

- Although the mechanism leading to LVNC is unclear, it is believed to be a disorder of endomyocardial morphogenesis. In normal circumstances, trabeculations in the fetal myocardial primordium occur at day 32 of embryonic development, before inverting ('compacting') by day 70. LVNC represents an arrest of this normal compaction process *in utero*, resulting in a layer of non-compacted myocardium lying adjacent to a compacted layer of endocardium.

Non-embryogenic hypothesis

- It has been suggested that this may be a direct result of mechanical loading conditions. This is supported by the fact that LVNC, in nearly three-quarters of women with the condition during pregnancy, resolves in the post-partum period. In the case of sickle cell disease, this may be as a result of the myocardial response to ↑ preload.

Clinical features

- The major clinical manifestations of LVNC are symptoms related to HF and atrial and ventricular arrhythmias.
- Systemic emboli due to stagnation of blood in the deep intertrabecular recesses can occur as a presentation or a complication of LVNC.

Reference

1. Arbustini E, Weidemann F, Hall JL. Left ventricular noncompaction: a distinct cardiomyopathy or a trait shared by different cardiac diseases? *J Am Coll Cardiol*. 2014;**64**:1840–50.

Left ventricular non-compaction: investigations and management

Investigations

- *ECG:* there are no specific features of LVNC; however, the ECG is frequently abnormal and may demonstrate TWI, arrhythmias, and conduction abnormalities.
- *Echocardiography:* may show the presence of multiple trabeculations, particularly at the apex, mid-inferior, and lateral walls (see Fig. 5.6). There may be multiple deep intertrabecular recesses communicating with the LV cavity, seen optimally on colour Doppler imaging and a 2-layered structure to the endomyocardium with a non-compacted and compacted layer. Other findings may include reduced LV systolic function, diastolic dysfunction, LV thrombi, and abnormal papillary muscle structure.
- LVNC may be seen together with other cardiomyopathies, including HCM, ACM, restrictive cardiomyopathy (RCM), and DCM.
- *Exercise testing:* with or without measurement of maximum ventilatory oxygen consumption—is useful to assess for arrhythmias and functional capacity.
- *Holter monitoring:* may identify arrhythmias or conduction abnormalities.
- *MRI:* may be useful to characterize trabeculations, particularly where echocardiographic images are suboptimal.

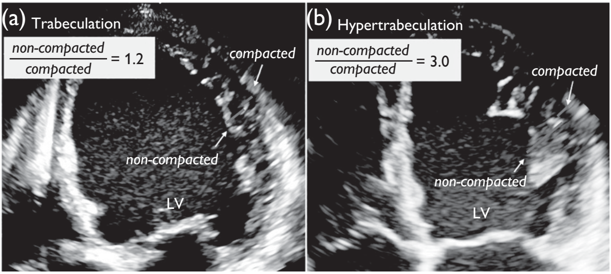


Fig. 5.6 Classical left ventricular non-compaction, as shown on echocardiography.

Reproduced from Arbustini E *et al*. *J Am Coll Cardiol* 2014; **64**(17):1840–50 with permission from Elsevier.

Diagnosis

- There is still debate over specific diagnostic criteria for LVNC.
- Echocardiographic criteria are based on the Jenni criteria, which proposed an end-systolic ratio of non-compacted:compacted layer of >2.
- MRI criteria include those proposed by Petersen *et al*. with a ratio of non-compacted:compacted layer of >2.3 in diastole.

Management

Heart failure

- HF should be managed with diuretics, ACEis, and β-blockers in the first instance (see ➔ Pharmacological management in chronic heart failure, p. 102).

Arrhythmias

- For management of specific arrhythmias, see ➔ Chapter 3.
- ICD/CRTD implantation may be effective in carefully selected individuals, but further work is required to assess safety and efficacy.

Anticoagulation

- Anticoagulation should be given to those with proven evidence of thrombus, prior embolic events, AF, or LVEF <45%.

Cardiac transplantation

- In severe cases, cardiac transplantation may be required. Cardiac transplantation is discussed in more detail in ➔ Mechanical circulatory support, p. 116; Heart transplantation: indications and work up, p. 120.

Follow-up

- Individuals should be followed up annually (to 2-yearly if stable) with ECG, echocardiography, Holter monitoring, and exercise testing.

Family screening

- First-degree relatives should be screened with ECG and echocardiography, beginning in childhood and then every 3 years thereafter.

Genetic testing

- Genetic testing may be helpful when LVNC is identified in relatives.
- If a gene is identified, the individual should be screened annually, with reduced frequency in adulthood if no phenotype is identified (every 3 years).

Restrictive cardiomyopathy: overview

Definition

- RCM is characterized by impaired diastolic function due to reduced ventricular compliance.

Epidemiology

- RCM is the least common cardiomyopathy and its prevalence varies according to the underlying cause.

Aetiology

Inherited

- Several genes have been identified in the pathogenesis of RCM. These include sarcomeric genes *TNNT2*, *TNN13*, α-actin (*ACTC*), and *MYH7*.

Acquired

These causes can be divided into infiltrative, storage, non-infiltrative, and endomyocardial.

Infiltrative

- Amyloidosis, sarcoidosis (see ➔ Cardiac amyloidosis, pp. 266–7; Cardiac sarcoidosis, pp. 270–1).

Storage

- Haemochromatosis (see ➔ Haemochromatosis, p. 272), Fabry disease (see ➔ Fabry disease, pp. 248–9), glycogen storage disorders.

Non-infiltrative

- Diabetic cardiomyopathy.
- Systemic sclerosis (see ➔ Systemic sclerosis, pp. 438–9).

Endomyocardial

- Consequence of chemotherapy and radiotherapy, endomyocardial fibrosis (EMF), tropical EMF, drugs (e.g. ergotamine, methysergide), hypereosinophilic syndrome, and carcinoid.

Clinical features

- Patients often have severely limited exercise tolerance due to inability to ↑ CO, as their SV is relatively fixed.
- They are also limited by breathlessness and have evidence of right HF (ascites, peripheral oedema, hepatomegaly).
- On examination, there may be a loud S_3 or S_4, or both may be present. There also may be prominent *x* and *y* descents of the JVP, and venous pressure may ↑ on inspiration (Kussmaul sign).
- Patients may also present with premature or recurrent AF due to atrial dilatation.

RCM: investigations and management

Investigations

- *ECG:* may show P mitrale or P pulmonale, reduced precordial QRS voltages, and atrial arrhythmias.
- *Echocardiography:* may demonstrate normal systolic function. Alternatively, systolic function may be reduced in advanced cases. A restrictive mitral inflow pattern is seen on Doppler tracing, suggestive of diastolic dysfunction. Infiltration may be evidenced by hypertrophied ventricles and thickened interatrial septum, and the myocardium may appear speckled. Bi-atrial enlargement is commonly seen.
- *MRI:* may aid in the diagnostic process.
- *EMB:* may be useful in establishing certain diagnoses.
- *Genetic testing:* may aid in diagnosis and need for family screening.

Management

- Treatment of the underlying condition.
- Diuretics are the mainstay of treatment; however, they may be challenging as patients with RCM often rely on high filling pressures, which can be negatively impacted by diuretics.
- CCBs and β-blockers may be introduced cautiously to ↑ filling time but may not be well tolerated.
- Similarly, the benefit of ACEis is not known and again these agents may not be well tolerated.
- Cardiac transplantation may be considered for certain individuals (see ➔ Mechanical circulatory support, p. 116; Heart transplantation: indications and work up, pp. 120–1).

Tropical endomyocardial fibrosis and hypereosinophilic syndrome

Tropical endomyocardial fibrosis

- *Epidemiology:* leading cause of RCM in the developing world, in particular Africa, Asia, and South America.
- *Aetiology:* may be caused by genetic predisposition, malnutrition, and parasitic infection (excessive immune response).
- *Basic pathology:* acute inflammation leads to oedema, infiltration of eosinophils, and necrosis. Thrombi may also line the endocardium. In chronic phases, endocardial thickening is caused by stimulation of cardiac fibroblasts and ↑ synthesis of collagen. Endomyocardial fibrous tissue deposition leads to RCM.
- *Clinical features:* begins with febrile illness, which may be associated with periorbital swelling, itching, and dyspnoea; RCM is more common.
- *Investigations:* eosinophilia may be detected in early stages of the disease. ECG may show non-specific changes. On echocardiography, infiltrates can be seen in the cardiac walls. Pericardial effusion is also a common finding. In the chronic phase of the condition, the picture is more that of RCM, involving both ventricles. MRI may also be useful to further characterize the condition. As echocardiography is almost always diagnostic, there is usually no need for invasive haemodynamic measurements.
- *Management:* EMF carries a very poor prognosis and there are no curative therapies thus far. HF is managed as per current HF guidelines. Surgery provides the option of endocardectomy and valve repair/replacement. Cardiac transplantation may also be considered in severe cases.

Hypereosinophilic syndrome

- *Basic pathology:* hypereosinophilic syndrome is defined as persistence of ≥ 1500 eosiniphils/mm^3. Overproduction of eosinophils can damage the myocardium through infiltration and release of inflammatory cytokines. This is followed by the development of mural thrombi. This leads onto fibrosis of the myocardium and ultimately to RCM.
- *Clinical features:* this condition can affect multiple organ systems, aside from its cardiac effects, including the skin, lungs, and GI, musculoskeletal, and nervous systems.
- *Investigations:* although ECG, echocardiography, and MRI are helpful, myocardial biopsy is the gold standard for diagnosis of cardiac involvement once other causes have been excluded.
- *Management:* if an individual has a *FIP1L1-PDGFRA* mutation, the first-line therapy is the tyrosine kinase inhibitor imatinib. Corticosteroids are generally considered first-line therapy if there is no gene identified. HF is managed as per current HF guidelines. Cardiac transplantation may also be considered in severe cases.

Cardiac amyloidosis: overview

Classification

- The three most common types of amyloidosis include light chain immunoglobulin (AL), wildtype transthyretin (ATTRwt), and mutant transthyretin (ATTRm) amyloidosis.

AL amyloidosis

- The prevalence of AL amyloidosis is around 3–9 cases per million/year.
- This is characterized by the production of monoclonal light chains (kappa/lambda), which can misfold. These can be derived from any B-cell dyscrasia (e.g. myeloma, lymphoma), although benign monoclonal gammopathies are most common.
- Cardiac involvement occurs in between 60% and 80% of patients.
- AL amyloidosis carries the worst prognosis.

ATTRwt cardiac amyloidosis

- ATTRwt cardiac amyloidosis, formally known as senile systemic amyloidosis, primarily occurs in elderly men.
- TTR is produced in the liver and normally acts as a transporter for thyroxine and retinol-binding protein.
- Although it acts as a tetramer, it can form monomers which have the potential to be amyloidogenic.
- Individuals live longer and tend to be less symptomatic.

ATTRm amyloidosis

- This is inherited in an AD fashion.
- The most common ATTR amyloid cardiomyopathy is due to the *Val122Ile* mutation (substitution of isoleucine for valine at position 122) and is more prevalent in African-Caribbean individuals, causing late-onset cardiomyopathy and progressive severe HF.
- Mutations in the *TTR* gene ↑ the chance of the tetramer forming the amyloidogenic monomers.

Other types of cardiac amyloid

- Amyloid A (AA amyloidosis) is a consequence of any chronic inflammatory condition that features a sustained acute phase response, causing elevated production of serum amyloid A protein. The most common causes are rheumatological conditions. Cardiac involvement is rare.

Basic pathology

- Amyloidosis is a clinical disorder characterized by extracellular deposition of insoluble fibril proteins.
- Amyloid deposition can occur in connective tissue or blood vessels, and in a variety of organs, including the heart, kidney, liver, and nervous system.
- Infiltration of the ventricular myocardium with amyloid fibrils is associated with reduced compliance and impaired myocardial relaxation. Left and right atrial pressures become progressively elevated, resulting in pulmonary oedema and peripheral volume overload. Endocardial involvement results in MR and TR, causing further ↑ in atrial pressures.

- Amyloid fibrils within the myocardium promote inflammation and fibrosis, and ↑ the propensity to fatal re-entrant arrhythmias.
- Atrial dilatation predisposes to AF. Direct involvement of the cardiac conduction tissue is associated with heart block and sudden death.
- Deposition of amyloid within coronary arteries is recognized and may be associated with angina or sudden death.
- Pericardial involvement is characterized by small effusions, which are usually of little clinical significance.

Clues to diagnosis

- In ATTRwt, there are usually lower rates of extracardiac involvement; however, more than half of patients have a history of carpal tunnel syndrome, which can precede cardiac involvement by up to a decade.
- In ATTRm and AL amyloidosis, extracardiac involvement is more common (nephropathy, neuropathy, and GI symptoms are most common).
- Liver involvement is seen more commonly in AL amyloidosis than in ATTRm, and these individuals also have a large tongue. Vitreous changes are more commonly seen in ATTRm.

Clinical features

- Common symptoms of RCM are listed in ➔ Clinical features, p. 262.

Cardiac amyloidosis: investigations and management

Investigations

- Common investigations are listed in the RCM section (see ➲ RCM: investigations and management, p. 263), in addition to the following.
- *Immunology:* serum immunoelectrophoresis and urinalysis for light chains to exclude underlying paraproteinaemia.
- *Echocardiography:* LVH tends to be concentric and may also involve the RV free wall and interatrial septum. The myocardium may appear 'speckled'; valves may be thickened and a pericardial effusion may be present. In all types of cardiac amyloid, global longitudinal strain (GLS) is generally preserved in the apical segments.
- *MRI:* LGE may be global, subendocardial, transmural, or focal.
- *Nuclear imaging:* technetium-labelled bisphosphonates (99mTc-DPD) bind more strongly with the myocardium in ATTR than in AL amyloidosis. This modality has a high specificity and a positive predictive value of 100% for ATTR amyloid.
- *Biopsy:* EMB may result in complications and therefore, a fat pad biopsy is usually preferable. Other areas that may be biopsied include the lip/rectum. A biopsy tends to have the highest yield in AL amyloidosis (80%), followed by ATTRm (67%) and ATTRwt (14%). For a positive result, the sample must show apple-green birefringence on Congo red staining. A bone marrow biopsy is performed, in addition, if there is a monoclonal protein on testing of the blood/urine. EMB is usually only performed in the absence of a positive biopsy.
- *DNA mutation analysis:* once a diagnosis is made, typing is required. If TTR is confirmed, DNA mutation analysis may be performed.
- The diagnostic algorithm for suspected amyloidosis is illustrated in Fig. 5.7.

Management

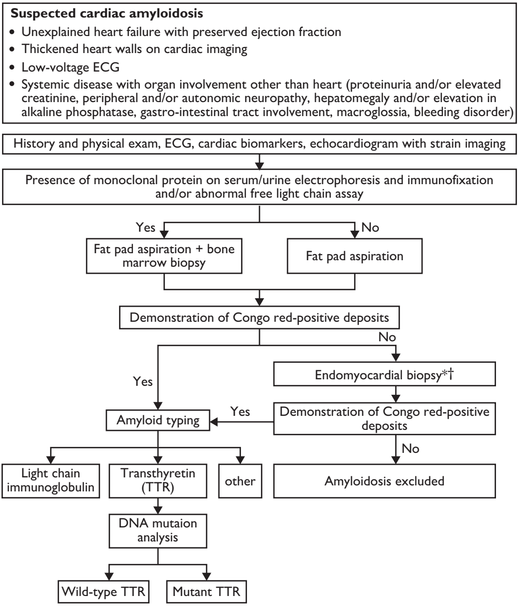
- General management measures are listed in the RCM section (see ➲ RCM: investigations and management, p. 263).
- Digoxin should be avoided in amyloid arrhythmia management, as this can bind to the fibrils and ↑ the risk of toxicity.
- Caution should be taken when using β-blockers or ACEis due to associated autonomic dysfunction in amyloidosis.

AL amyloidosis

- The first-line therapy is autologous stem cell transplantation.
- In those aged >70 years, who are NYHA class III/IV and with multiple organ involvement (>3), chemotherapy (combination of melphalan and dexamethasone) is indicated.
- Immunomodulatory drugs (lenalidomide) may also be added.
- Heart transplantation is infrequently considered due to multiorgan involvement and the risk of recurrence in the transplanted heart.

ATTR amyloidosis

- Liver transplantation is the most established treatment strategy.
- Other pharmacological options include:
  - Patisiran is a small interfering ribonucleic acid (siRNA), which is given IV. A recent randomized controlled trial[1] showed significant ↑, compared with placebo, in neurology and quality of life.


Suspected cardiac amyloidosis
• Unexplained heart failure with preserved ejection fraction
• Thickened heart walls on cardiac imaging
• Low-voltage ECG
• Systemic disease with organ involvement other than heart (proteinuria and/or elevated creatinine, peripheral and/or autonomic neuropathy, hepatomegaly and/or elevation in alkaline phosphatase, gastro-intestinal tract involvement, macroglossia, bleeding disorder)
History and physical exam, ECG, cardiac biomarkers, echocardiogram with strain imaging
Presence of monoclonal protein on serum/urine electrophoresis and immunofixation and/or abnormal free light chain assay
Yes
No
Fat pad aspiration + bone marrow biopsy
Fat pad aspiration
Demonstration of Congo red-positive deposits
No
Endomyocardial biopsy*†
Yes
Yes
Amyloid typing
Demonstration of Congo red-positive deposits
No
Light chain immunoglobulin
Transthyretin (TTR)
other
Amyloidosis excluded
DNA mutaion analysis
Wild-type TTR
Mutant TTR

* Alternatively other source tissue (lip, rectum, suspected involved organ other than heart) can be obtained but if negative for Congo red desposits than endomyocardial biopsy should be attempted

† In suspected ATTR cardiac amyloidosis, the use of bone scintigraphy can replace the need for endomyocardial biopsy for diagnostic confirmation

Fig. 5.7 Diagnostic algorithm for suspected amyloidosis.

Reproduced from Muchtar E, *et al*. *Circulation Research* 2017; **121**:819–37 with permission from Wolters Kluwer Health, Inc. Copyright © 2017 American Heart Association, Inc. https://www.ahajournals.org/doi/full/10.1161/circresaha.117.310982#d3848102e1

- Inotersen is an antisense oligonucleotide drug, administered s/c, which acts to inhibit TTR in the liver. In another randomized controlled trial,[2] this also showed significant benefits, compared with placebo, in ↑ neurology and quality of life. Importantly, this can lead to thrombocytopenia and therefore requires careful monitoring.
- Tafamidis, which binds to TTR and stabilizes the tetrameric structure, has also shown promise. In the ATTR-ACT trial,[3] this was associated with ↓ all-cause mortality and cardiac-related hospital admissions, ↓ functional decline, and ↑ quality of life.

References

1. Adams D, Gonzalez-Duarte A, O'Riordan WD, *et al*. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;**379**:11–21.
2. Benson MD, Waddington-Cruz M, Berk JL, *et al*. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;**379**:22–31.
3. Maurer MS, Schwartz JH, Gundapaneni B, *et al*. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;**379**:1007–16.

Cardiac sarcoidosis

Epidemiology

- The prevalence is around 0.16%.
- Sarcoidosis commonly affects young and middle-aged adults, and occurs more commonly in black than in white individuals.

Aetiology

- The cause of sarcoid is unknown.

Basic pathology

- This is an inflammatory condition characterized by non-caseating granulomas with multinucleate giant cells in the centre.
- CD4 lymphocytes are found throughout the granuloma, whereas CD8 lymphocytes cluster at the periphery.
- Sarcoidosis can affect multiple organs, most commonly presenting with bilateral hilar lymphadenopathy, lung infiltrates, skin lesions (erythema nodosum and lupus pernio), and uveitis. Other organs may also be affected, including the heart, kidneys, nervous system, liver, spleen, joints, muscles, and bone marrow.

Clinical features

- Individuals may commonly be asymptomatic.
- If an individual is symptomatic, the symptoms are usually related to the location of inflammation.
- In cardiac sarcoid, the most common presentation is symptoms and signs of end organ dysfunction, with conduction disease, CHB, arrhythmia, HF, or sudden death. Chest pain can also occur if granuloma infiltrate the coronary arteries.
- Other symptoms may include tiredness, weight loss, low-grade fever, cough, and dyspnoea. Individuals may also present with skin lesions, photophobia, and arthritis.

Investigations

- Common investigations are listed in the RCM section (see ➔ RCM: investigations and management, p. 263), in addition to the following.
- *Lymphocyte count:* may also demonstrate lymphopenia, particularly during acute episodes of sarcoidosis.
- *Serum ACE:* this is elevated in half of all individuals.
- *ECG:* conduction abnormalities may be the presenting sign of sarcoidosis in those aged <60 years. VT is the most common arrhythmia.
- *Holter monitoring:* essential for early detection of arrhythmias.
- *MRI:* LGE is usually found in a subepicardial or transmural distribution. T1 and T2 mapping may also provide supportive evidence of cardiac involvement.
- *Cardiac fluorodeoxyglucose (FDG)-PET:* this can demonstrate focal areas of FDG uptake. Whole-body FDG-PET may be used to identify areas that may be amenable for biopsy. Serial FDG-PET scans may be used to assess response to therapy.

- *EMB:* this is the gold standard for diagnosis; however, due to the patchy nature of the disease, the sensitivity is low. In those with extracardiac sarcoidosis, lung or lymph node biopsy is usually undertaken.

Diagnosis

- Although the criteria are not validated, the Heart Rhythm Society (HRS) 2014 Consensus Statement supports a definite diagnosis if there are non-caseating granulomas on EMB and no other cause found.
- Cardiac sarcoid is probable if there is a histological diagnosis of extracardiac sarcoid and one or more of the following is present:
  - Cardiomyopathy responsive to steroid ± immunosuppression
  - Unexplained LVEF <40%
  - Unexplained spontaneous/induced VT
  - Mobitz type II/CHB
  - Patchy uptake on cardiac PET
  - LGE on MRI
  - Positive gallium-67 uptake
  - Exclusion of other causes.

Prognosis

- Variable and most linked to the magnitude of LV dysfunction, arrhythmia, or conduction disease. CT-PET and MRI abnormalities also infer an adverse prognosis

Management

- General management measures are listed in the RCM section (see ➔ RCM: investigations and management, p. 263). A multispecialty approach to management should be adopted, including cardiologists and pulmonologists, amongst others, in order to meet patient care needs.
- *Corticosteroids:* are the mainstay of treatment and should be considered in symptomatic patients with signs of inflammation and any one of the following: reduced LVEF, high-grade AV block, frequent ectopy, NSVT/VT/VF. Methotrexate, azathioprine, mycophenolate, and ciclosporin may be used as steroid-sparing agents.
- *Antiarrhythmic therapy:* for management of specific arrhythmias, see ➔ Chapter 3. Amiodarone may be useful but are generally avoided long term due to side effects. Ablation may be useful for some patients.
- *Device implantation:* up to 20% of individuals with heart block may develop arrhythmia. Therefore, ICD implantation should be the preferred device choice if a pacemaker is required.
- *Cardiac transplantation:* may be recommended in end-stage disease or in intractable arrhythmias (see ➔ Mechanical circulatory support, p. 116; Heart transplantation: indications and work up, p. 120).

Haemochromatosis

Epidemiology

- Around 1 in 10 individuals in the United States is heterozygous for the causative mutation, and 1 in 200 is homozygous (although this does not always translate to clinical disease).

Aetiology

- This is an autosomal recessive condition.
- The most common mutation is *HFE C282Y* on chromosome 6 (>90% of cases).

Basic pathology

- This is caused by ↑ absorption of iron, which can lead to accumulation in organs, causing dysfunction.

Clinical features

- Common symptoms of RCM (occurring in 15–20%) are listed in ➲ Clinical features, p. 262.
- In addition, individuals may demonstrate:
  - Hepatomegaly
  - Hyperpigmentation
  - Diabetes
  - Arthritis
  - Hypogonadism.

Investigations

- Common investigations are listed in the RCM section (see ➲ RCM: investigations and management, p. 263), in addition to the following.
- *Bloods:* if serum ferritin is elevated and transferrin saturation ≥45%, genetic studies should be performed.
- *MRI:* T2* relaxation times are useful to assess the amount of iron deposition in the heart.
- *Genetic testing:* this is performed for the *HFE C282Y* mutation in the first instance, with other mutations subsequently tested.

Management

- General management measures are listed in the RCM section (see ➲ RCM: investigations and management, p. 263).
- Therapeutic phlebotomy is repeated until transferrin saturation is <50%.
- Chelation therapy may be considered in those who are anaemic and those with severe heart disease or poor venous access.
- Vitamin C supplementation should be avoided, as this can ↑ dietary absorption of iron.

Muscular dystrophies

- Muscular dystrophies (MDs) are a group of hereditary muscle disorders characterized by progressive skeletal muscle weakness.
- The best characterized conditions include DMD and BMD, limb-girdle (LGMD), facioscapulohumeral (FSH), myotonic, and Emery–Dreifuss (EDMD) muscular dystrophies.

Basic pathology

- The pathophysiology of cardiomyopathy is similar in all of the conditions. There is absence or impairment in function of proteins, which are required for myocyte function.
- This also affects proteins which are involved in maintaining muscle fibre integrity, leading to fragility of the sarcolemmal membrane and muscle damage.
- Over time, failure to repair damage leads to necrosis and replacement with fibrofatty tissue. If this occurs in the conduction system, this can lead to conduction abnormalities.
- The pathological process may lead to DCM, HCM, or RCM.

Duchenne and Becker muscular dystrophy

- These are X-linked disorders of the dystrophin gene.
- DMD presents in childhood and is the most common hereditary MD, with near-complete absence of the sarcolemmal membrane protein dystrophin on biopsy.
- Most individuals lose their ability to walk by the age of 12 years and require ventilatory support by 25 years. There has been significant improvement in survival in this condition, with some individuals now living past 40 years.
- BMD presents in adulthood, with reduced dystrophin levels on biopsy. This is associated with less severe skeletal muscle involvement, but often more severe cardiac muscle involvement.
- Cardiac abnormalities in both conditions include sinus arrhythmia, atrial and ventricular ectopics, supraventricular arrhythmias, AV conduction block, and BBB, as well as LV dysfunction.

Myotonic dystrophy 1 and 2 (MD1, MD2)

- These are AD multisystem disorders caused by a CTG trinucleotide repeat defect in the gene encoding myotonin.
- Conduction abnormalities are common, as are atrial and ventricular arrhythmias. Individuals may also have LV dysfunction.
- Those with DM1 are at higher risk of SCD.

Emery–Dreifuss muscular dystrophy

- This is an X-linked disorder (EDMD1) but may also demonstrate AD (EDMD2) and rarely autosomal recessive inheritance.
- EDMD is caused by mutations in lamin A and lamin C (nuclear envelope proteins), with absence of emerin on biopsy.
- Muscle weakness has a humeral and peroneal distribution. Cardiac manifestations include AV conduction abnormalities and atrial arrhythmias. SCD due to ventricular tachyarrhythmia may also occur.

Limb-girdle muscular dystrophy

- This can be inherited in an AD or recessive manner. Mutations occur in genes encoding proteins of the nuclear envelope in skeletal muscle. This tends to affect the shoulder and pelvic girdle muscles.
- Cardiac involvement is particularly predominant in LGMD1B (laminopathy), LGMD2E, and LGMD2I, including cardiomyopathy, conduction system disease, and an ↑ risk of SCD.

Facioscapulohumeral muscular dystrophy

- This is an AD MD, with progressive involvement of the facial, shoulder, and hip girdle muscles.
- Cardiac manifestations include conduction delay, as well as supraventricular and ventricular arrhythmias.

Investigations

- Routine screening for cardiomyopathies (see ➔ Family screening, p. 239), in addition to the following.
- *CK:* 50–100 times normal.
- *Genetic testing.*
- *EMG and muscle biopsy:* if genetics are negative. An EMG may show fast-firing, short-duration, polyphasic, and ↓ amplitude motor units, demonstrating early recruitment in the diseased muscle.

Management

- Multispecialty care is recommended, including cardiologists, neurologists, and pulmonologists, amongst others, to meet the care needs of these patients.
- Once a diagnosis of cardiomyopathy is made, standard HF treatment with diuretics, ACEis, and β-blockers is required (see ➔ Pharmacological management in chronic heart failure, p. 102).
- β-blockers should be used with caution where there are conduction abnormalities, particularly in individuals without a device with pacing capabilities.
- ICD therapy may be considered in those at high risk of SCD, especially if there is already a pacing indication.

Takotsubo cardiomyopathy: overview

Definition

- Takotsubo cardiomyopathy takes its name from the Japanese word for an octopus trap due to the shape adopted by the LV at the end of systole. It is usually triggered by emotional and physical triggers, and often shares similar clinical features with ACS, including ECG changes and raised cardiac biomarkers.

Epidemiology

- The incidence of Takotsubo cardiomyopathy is between 1% and 3% in men and between 5% and 6% in women presenting with STEMI.

Basic pathology

- Sympathetic stimulation is thought to be central to the pathogenesis of Takotsubo cardiomyopathy. The manner in which this catecholamine ↑ leads to Takotsubo cardiomyopathy is based on several possibilities:
  - Epicardial spasm
  - Microcirculatory dysfunction
  - Direct toxicity on myocytes.

Aetiology

Predisposing factors

Hormones

- Given the large number of post-menopausal women affected, it has been suggested that lower levels of oestrogen may play a role. Women over the age of 55 years have a 5-fold ↑ risk of developing Takotsubo cardiomyopathy, compared with those below the age of 55 years, and a 10-fold ↑ risk when compared with men.
- Phaeochromocytoma is a neuroendocrine tumour (enterochromaffin cells of the adrenal gland), which leads to the release of large amounts of catecholamines that can result in LV dysfunction.

Psychiatric and neurological conditions

- Takotsubo cardiomyopathy may occur after stroke, seizures, and subarachnoid haemorrhage.
- Anxiety and depression are more common in those with Takotsubo cardiomyopathy, with a higher prevalence of type D personality which is associated with inhibition and negative emotions.

Genetics

- There have been some familial cases of Takotsubo cardiomyopathy.

Triggers

(One-third have no preceding event.)

- *Emotional:* grief, fear, anger, conflicts.
- *Physical:* strenuous physical activity, undergoing medical procedures, acute medical conditions, pregnancy, stress testing, EP testing.

Takotsubo cardiomyopathy: clinical features and investigations

Clinical features

- Patients usually present with chest pain, shortness of breath, palpitations, and syncope.
- Symptoms may be indistinguishable from those seen with acute MI.
- Some patients may present with symptoms of HF, life-threatening arrhythmias, cardiogenic shock, or even cardiac arrest.

Investigations

- *Bloods:* Takotsubo cardiomyopathy is usually associated with high levels of troponin and NT-proBNP.
- *ECG:* normally demonstrates ST-segment elevation and/or TWI and QT prolongation which may be widespread. This is often not confined to a single region.
- *Echocardiography:* enables identification of regional wall motion abnormalities. In the case of apical ballooning, the basal segments may be hyperkinetic, leading to dynamic LVOTO, which may also be associated with MR due to SAM of the mitral leaflet.
- *Coronary angiography:* any individual presenting with ST-segment elevation on their ECG should undergo urgent coronary angiography. The gold standard to diagnose Takotsubo cardiomyopathy is with left ventriculography during coronary angiography. Four different forms of Takotsubo cardiomyopathy (see Fig. 5.8) may be seen:
  - Apical ballooning (this is the most common form)
  - Mid-ventricular
  - Basal
  - Focal.
- *CTCA:* may provide valuable information if the patient is unable to undergo invasive coronary angiography. This may also be useful in patients who have recurrent Takotsubo cardiomyopathy.
- *MRI:* is useful for differentiating Takotsubo cardiomyopathy from ACS where a single coronary artery territory appears to be affected, as there will be evidence of myocardial oedema, but no LGE. MRI also enables optimal visualization of the RV, which can rarely also be affected in Takotsubo cardiomyopathy.

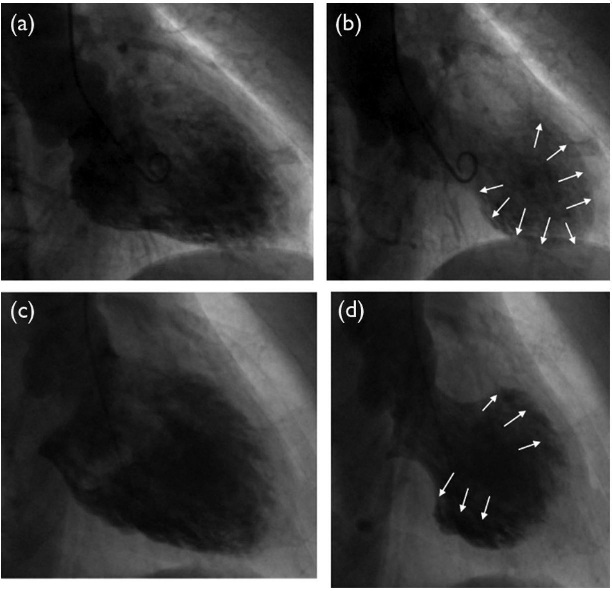


Fig. 5.8 Forms of Takotsubo cardiomyopathy. (a, b) Typical type of Takotsubo cardiomyopathy showing akinesis in the mid and apical portions of the left ventricular chamber, along with hypercontraction of the basal left ventricle (a: diastole; b: systole). (c, d) Atypical type of Takotsubo cardiomyopathy in which the left ventricular apex is not affected (c: diastole; d: systole).

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Takotsubo cardiomyopathy: management and prognosis

Prognosis

- The condition is transient, leading to full recovery. Recovery usually occurs within 8 weeks.
- The recurrence rate is around 1.8% per patient-year.
- Patients may demonstrate different types of Takotsubo cardiomyopathy on each presentation.

Management

Haemodynamically stable Takotsubo cardiomyopathy

- Monitoring for 48h on CCU and administration of β-blocker and ACEi.

Heart failure/pulmonary oedema

- See ➲ Management of acute heart failure, pp. 108–11.

Hypotension/shock

- See ➲ Management of acute heart failure, pp. 108–11.
- See ➲ Mechanical circulatory support, p. 116; Heart transplantation: indications and work up, pp. 120–1.
- It is important to avoid inotropes where possible. Levosimendan has been proposed as an alternative inotrope to catecholamine-based agents in these patients, with higher mortality rates reported in the latter.
- In patients with LVOTO, consider IV fluid and a β-blocker. It is important to avoid diuretics and agents that may significantly drop the afterload such as nitrates. An IABP is also contraindicated.

Arrhythmias

- In the case of arrhythmias, a β-blocker is preferred. If the patient develops heart block, temporary RV pacing should be considered.
- QT-prolonging drugs should be avoided to prevent TdP, and permanent devices should also be avoided, given the likelihood of recovery. If there is evidence of life-threatening arrhythmias or significant prolongation of the QT interval, a life vest (wearable defibrillator) should be considered.

Thrombus/thromboembolism

- An oral anticoagulant should be commenced and reviewed at follow-up.

Longer-term follow-up

- Continue β-blocker and ACEi for at least 3 months or until full recovery is seen at follow-up.

Nutrition deficiency and cardiac effects

Thiamine deficiency (beriberi)

Epidemiology

- This is between 0.1% and 1%. This is most common in East Asia.

Aetiology

- Inadequate intake, particularly in East Asian people subsisting on highly polished rice. Milling removes the thiamine-containing husk.
- Diet rich in thiaminases (e.g. nuts, tea, coffee, fermented fish).
- Malabsorption such as secondary to GI surgery.
- Recurrent diarrhoea and vomiting.
- Alcohol abuse (alcohol blocks the transport mechanism for absorption of thiamine). This may be exacerbated by magnesium deficiency, which is required for appropriate thiamine function.
- Malignancies, in particular those of haematological origin, may lead to thiamine deficiency through ↑ consumption by cancer cells.

Basic pathology

- Thiamine pyrophosphate is involved in carbohydrate metabolism and is dependent on thiamine for its function.
- The brain and nerve cells rely on glucose, and therefore, thiamine deficiency can lead to cell damage.
- Myocytes can employ fatty acid oxidation as an energy source; myocytes are only damaged if there is also a deficiency in fatty acids.

Clinical features

- Thiamine deficiency may present in several ways.
- Wernicke encephalopathy (most commonly as a result of alcohol abuse), which presents as a triad of ataxia, nystagmus, and confusion.
- *Wet beriberi:* high-output cardiac failure with tachycardia, a wide pulse pressure, sweating, and warm skin.
- *Shoshin beriberi:* low-output cardiac failure characterized by severe hypotension, lactic acidosis, and low systemic vascular resistance. Wet and Shoshin beriberi can occur in acute or chronic deficiency.
- *Dry beriberi:* due to chronic deficiency; causes distal peripheral neuropathy.

Investigations

- Before thiamine replacement, a blood sample should be taken for levels of erythrocyte thiamine pyrophosphate, a marker of thiamine stores. Results may take several days; do not delay treatment.
- Individuals should also be assessed for concomitant deficiencies, in particular magnesium deficiency, as well as that of calcium and phosphate.
- All patients should undergo TFTs if there is evidence of high-output failure.
- Lactate levels may be elevated.
- Echocardiography should be done to assess ventricular function.
- MRI of the head may detect changes which are suggestive of Wernicke's encephalopathy, including ↑ T2 signal in the midline cerebellum, thalamus, or hypothalamus periaqueductal region.

Prognosis

- *Wernicke's encephalopathy:* untreated, 20% of individuals die.
- *Wet beriberi:* without treatment, this can lead to death; early treatment can lead to improvement within 24h.
- *Dry beriberi:* with treatment, symptoms usually improve within weeks/months if there are no additional neuropathy contributors.

Management

- High-dose IV thiamine should be administered for 3 days.
- If there is a clinical response, this can be continued for a further 5 days at a lower dose and discontinued if there is no response.

Selenium deficiency

Epidemiology

- More common in China where the soil is extremely deficient in selenium, affecting between 0.5 and 1 billion individuals worldwide.

Aetiology

- Selenium deficiency is usually rare in healthy individuals.
- Deficiency occurs in those with GI pathology such as those on long-term parenteral feeding or post-gastric bypass.
- Levels may also be ↓ in those on dialysis or infected with HIV.

Basic pathology

- Selenium is involved in reoxidation of reduced glutathione and has close metabolic interrelationships with vitamin E.
- It is part of the enzyme glutathione peroxidase, which is thought to destroy peroxides derived from unsaturated fatty acids.

Clinical features

- Fatal cardiomyopathy cases have been due to selenium deficiency.
- VT and VF are also associated with selenium deficiency.
- In China, Keshan disease, a childhood cardiomyopathy, has been attributed to selenium deficiency.

Investigations

- Selenium blood levels.
- Individuals should also be assessed for concomitant deficiencies, in particular magnesium deficiency, as well as that of calcium and phosphate.

Management

- PO selenium supplementation may reverse complications.

Electrolyte abnormalities

- *Chronic hypocalcaemia:* associated with HF that responds to restoration of serum Ca^{2+}. Rapid blood transfusion (citrated blood) may result in transient LV dysfunction, due to ↓ serum Ca^{2+}.
- *Hypophosphataemia* (severe): can also result in reversible LV impairment, restored by correcting phosphate levels.
- *Hypomagnesaemia:* associated with SVT and VT (especially in the context of digitalis toxicity), and focal myocardial necrosis is seen.

Myocarditis: overview

Definition

- Myocarditis is defined as an 'inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria'.[1]

Epidemiology

- The incidence of myocarditis remains difficult to determine, given that most patients do not undergo EMB.
- In those with non-ischaemic DCM, the incidence of myocarditis on biopsy is around 9–16%.

Basic pathology

- In the majority of cases, an organism enters the myocardium, which leads to immunological activation.
- CD4+ cells and B cells are activated, and macrophages, natural killer cells, and other inflammatory cells infiltrate the myocardium where they release cytokines, resulting in further inflammatory cell infiltration and leading to myocyte lysis.
- Direct or indirect damage through non-infectious aetiological factors also leads to cell death. Exposure of the immune system to antigens to which it is not normally exposed results in the production of anti-heart antibodies.
- The proposed pathological processes are illustrated in Fig. 5.9.

Reference

1. Ferreira VM, Schulz-Menger J, Holmvang G, *et al*. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol*. 2018;**72**:3158–76.

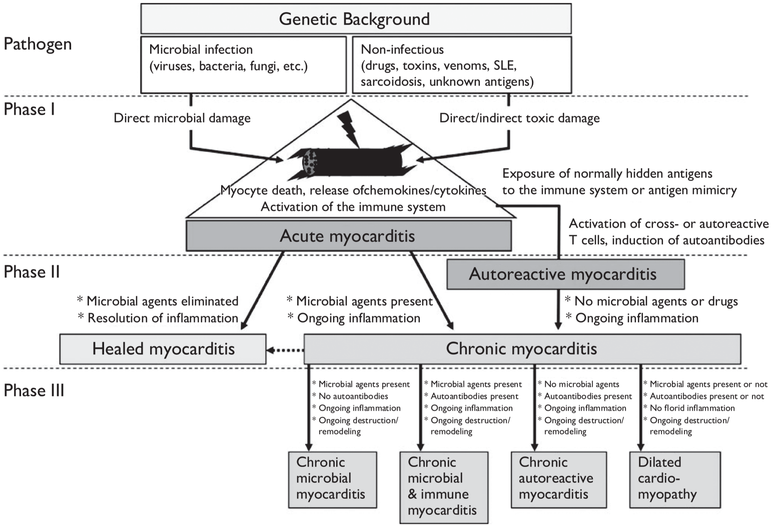
Genetic Background
Pathogen
Microbial infection (viruses, bacteria, fungi, etc.)
Non-infectious (drugs, toxins, venoms, SLE, sarcoidosis, unknown antigens)
Phase I
Direct microbial damage
Direct/indirect toxic damage
Myocyte death, release ofchemokines/cytokines
Activation of the immune system
Exposure of normally hidden antigens to the immune system or antigen mimicry
Activation of cross- or autoreactive T cells, induction of autoantibodies
Acute myocarditis
Phase II
Autoreactive myocarditis
* Microbial agents eliminated
* Resolution of inflammation
* Microbial agents present
* Ongoing inflammation
* No microbial agents or drugs
* Ongoing inflammation
Healed myocarditis
Chronic myocarditis
Phase III
* Microbial agents present
* No autoantibodies
* Ongoing inflammation
* Ongoing destruction/ remodeling
* Microbial agents present
* Autoantibodies present
* Ongoing inflammation
* Ongoing destruction/ remodeling
* No microbial agents
* Autoantibodies present
* Ongoing inflammation
* Ongoing destruction/ remodeling
* Microbial agents present or not
* Autoantibodies present or not
* No florid inflammation
* Ongoing destruction/ remodeling
Chronic microbial myocarditis
Chronic microbial & immune myocarditis
Chronic autoreactive myocarditis
Dilated cardio- myopathy

Fig. 5.9 Proposed pathological processes leading to myocarditis.

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Myocarditis: aetiology and clinical features

Aetiology

Infection

- *Viral:* adenovirus, Coxsackie virus, echovirus, influenza A and B, hepatitis C, parvovirus B19, CMV, EBV, HHV, HIV, VZV.
- *Bacterial: Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Haemophilus influenzae*, *Mycobacterium*, *Corynebacterium diphtheriae*, typhoid.
- *Spirochaetal: Borrelia burgdorferi* (Lyme disease), *Leptospira* (Weil disease), syphilis.
- *Rickettsial: Coxiella burnetii* (Q fever), *Rickettsia rickettsii.*
- *Fungal: Aspergillus*, *Candida*, *Cryptococcus*.
- *Protozoal: Trypanosoma cruzi*, *Toxoplasma gondii* (for further information, see ➔ Infectious causes of myocarditis, pp. 290–2).

Immune-mediated

- *Allergens:* vaccines, tetanus toxoid, antibiotics (penicillins, cephalosporins, sulfonamides), antiepileptics (carbamazepine, phenytoin, thiazides), lithium.
- *Alloantigens:* rejection of cardiac transplant.
- *Autoantigens:* infection-negative giant cell (giant cell myocarditis), infection-negative lymphocytic myocarditis, SLE, rheumatoid arthritis, scleroderma, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, sarcoidosis, polymyositis/dermatomyositis (see ➔ Cardiac sarcoidosis, pp. 270–1).

Toxic

- *Drugs:* cocaine, amphetamines, anthracyclines.
- *Physical agents:* radiation.

Clinical features

- Clinical consequences of the damage can range from asymptomatic subclinical infection to rapidly progressive and ultimately fatal.
- Symptoms may be experienced in isolation or as a combination, including: chest pain, shortness of breath, reduced exercise tolerance, PND, orthopnoea, oedema, fatigue, palpitations, dizziness, and loss of consciousness.
- This may present as an ACS-type syndrome with acute-onset chest pain (which may recur) usually 1–4 weeks following a respiratory or GI illness. It is also important to consider whether the patient is in the post-partum period.
- This may also present with HF symptoms over a few weeks to months or with a more chronic picture lasting over 3 months.
- In more serious cases, it may present with life-threatening arrhythmias or cardiogenic shock.

Myocarditis: investigations

Investigations

- *Bloods:* FBC, U&Es, LFTs, NT-proBNP—may be raised (does not exclude myocarditis if normal); troponin—may be raised (does not exclude myocarditis if normal); erythrocyte sedimentation rate (ESR)/CRP—may be raised (does not exclude myocarditis if normal); antinuclear antibodies (ANA)/antineutrophil cytoplasmic antibodies (ANCA)/extractable nuclear antigen (ENA)/rheumatoid factor (RF), ACE.
- *Serology:* generally unhelpful due to high background seropositive rates. Individuals should be tested for HIV and where there has been recent travel/high suspicion of Lyme/rickettsial/protozoal disease.
- Anti-cardiac antibodies (if available).
- *ECG:* conduction abnormalities, ST–T wave changes, arrhythmias.
- *Echocardiography:* to assess ventricular size and function, and wall motion abnormalities, as well as to assess the valves and pericardium and for the presence of pericardial effusion.
- *Holter monitoring:* arrhythmias, conduction abnormalities.
- *MRI:* allows more in-depth tissue characterization and identification of signs of acute inflammation (oedema on T2-weighted images), as well as scar (LGE on T1-weighted images). The Lake Louise criteria are typically used to form a diagnosis (see Box 5.5).
- *Coronary angiography:* may be performed in order to exclude CAD.
- *CT-PET:* can detect acute inflammation and disease extent, and guide targeted EMB.
- *EMB:* the diagnosis is suspected based on the clinical picture and one or more abnormalities in cardiac enzymes (troponin)/ECG/functional and structural abnormalities on echocardiography/MRI, as well as on tissue characterization on MRI. EMB is the diagnostic gold standard for myocarditis but is currently recommended in a limited number of clinical scenarios.
- EMB must be performed in a centre with appropriate expertise. The complication rate in experienced hands is low (≤0.8%). At least three samples (1–2mm) should be taken. The tissue obtained should be histologically and immunohistochemically examined. Viral polymerase chain reaction (PCR) should also be performed and a peripheral blood sample taken simultaneously to assess for systemic infection.

NB exercise testing should be avoided in the acute phase due to the risk of provoking arrhythmias.

Box 5.5 Updated 2018 Lake Louise criteria for diagnosis of myocarditis

- In those with significant clinical pre-test probability, myocarditis is confirmed by the presence of the following:
  - Regional or global ↑ in native T2 *OR* regional or global ↑ in T2 signal intensity *AND* regional or global ↑ in native T1 *OR* regional or global ↑ in ECV *OR* regional LGE signal ↑.

ECV, extracellular volume; LGE, late gadolinium enhancement.

Myocarditis: management and prognosis

Prognosis

- In around 50% of cases, myocarditis resolves within the first 2–4 weeks. In 25% of cases, myocarditis may progress to DCM. Overall prognosis is dependent on the underlying diagnosis and is variable.

Management

- Management of patients with myocarditis is largely supportive.

Haemodynamic instability

- Patients should be managed for acute HF (see ➔ Management of acute heart failure, pp. 108–11). In some patients with haemodynamic instability, ECMO/VAD may be required as a bridge to recovery or to transplantation (see ➔ Mechanical circulatory support, p. 116 ; Heart tranplantation: indications and work up, pp. 120–1).

Stable patients

- Patients should be admitted until a diagnosis is confirmed. HF should be managed with diuretics, ACEis, and β-blockers in the first instance (see ➔ Pharmacological management in chronic heart failure, p. 102).

Arrhythmias

- For management of specific arrhythmias, see ➔ Chapter 3. ICD implantations should be deferred until after recovery from the acute phase. In those with ventricular arrhythmias, a life vest should be considered.

Immunosuppressive therapy

- Active infection should be ruled out on EMB prior to immunosuppression. Immunosuppressive therapy (steroids, azathioprine) may be considered when myocarditis is thought to be a cardiac manifestation of an extracardiac autoimmune condition (giant cell myocarditis, cardiac sarcoidosis).

Follow-up

- Patients should be discharged when they are stable and their cardiac enzymes have returned to normal. Physical activity should be avoided until resolution of the condition. Ideally repeat assessment should be performed at 6 months before advice to resume activities.
- All individuals should undergo long-term follow-up in the outpatient setting with ECG and echocardiography. In the event of persistently raised cardiac enzymes or a reduction in ventricular function, patients should be reassessed with cardiac MRI, PET-CT, or EMB.

Infectious causes of myocarditis

Viral myocarditis

Coxsackie virus

- In Western countries, Coxsackie virus is a common cause of myocarditis.
- Usually mild/self-limiting, can be virulent in neonates/children.
- Clinical features include myalgia, upper respiratory tract symptoms, pleuritic chest pains, palpitations, arthralgia, myalgia, and fever.
- Diagnosis is made on viral culture from a throat swab or stool.
- Most make an uneventful recovery within weeks.
- Treatment is symptomatic.

HIV

- Cardiac involvement is common in patients with HIV.
- The usual presentation is with HF symptoms and DCM, due to a direct effect of HIV on the myocardium. Opportunistic infection in acquired immune deficiency syndrome is another cause of myocarditis.

Bacterial myocarditis

Diphtheria

- This occurs in those who have not been vaccinated and who have travelled to areas where diphtheria is endemic.
- Clinical features include low-grade fever and sore throat, with lymphadenopathy, dysphonia, dysphagia, cough, and dyspnoea. A brown-greyish membrane may cover the tonsils, pharynx, and larynx.
- Myocarditis is seen in 10–20%, as the toxin halts protein synthesis.
- HF features appear towards the end of the first week.
- Diagnosis is made from bacterial cultures from nose/throat swabs.
- Treatment with antitoxin should be given early in the disease course.

Tuberculosis

- Tuberculous myocarditis is rare unless there is pericarditis (see ➔ Tuberculous pericarditis, pp. 304–5).

Rickettsial myocarditis

Coxiella burnetti (Q fever)

- Contracted through inhalation/ingestion of aerosolized particles from close contact with animals.
- Presents with a flu-like illness, headache, cough, and myalgia.
- Cardiac features include myocarditis, pericarditis, and endocarditis.
- This is diagnosed by using an indirect immunofluorescence assay.
- In most patients, the condition is self-limiting and resolves within ~2 weeks. Doxycycline may limit the duration of the infection.

Rickettsia ricketsii (Rocky Mountain spotted fever)

- Transmitted by an infected tick bite, common in North America.
- Symptoms include fever, rash, headache, myalgia, abdominal pain, diarrhoea, and vomiting.
- This is diagnosed by using an indirect immunofluorescence assay.
- This produces widespread vasculitis that involves the myocardium.
- Doxycycline should be started as soon as the diagnosis is confirmed.

Spirochaetal myocarditis

Borrelia burgdorferi (Lyme disease)

- Lyme disease is transmitted by a tick bite.
- A typical lesion (erythema migrans) develops at the site of the bite. Fever, headache, myalgia, and arthralgia also occur.
- About 10% of patients have evidence of cardiac involvement. AV conduction abnormalities and LV dysfunction are common. Syncope due to CHB is frequent.
- This is diagnosed on immunofluorescence assay.
- Patients with second- or third-degree heart block require hospital admission and monitoring. Treat with amoxicillin/doxycycline and temporary pacing (if required). In severe disease, IV benzylpenicillin is advised.

Leptospirosis (Weil disease)

- Spreads through contamination with urine from infected animals.
- This can lead to a flu-like illness, jaundice, renal failure, haemorrhage, and meningitis.
- Cardiac involvement is seen in more severe presentations. Interstitial myocarditis with involvement of the papillary muscles is seen; conduction defects, aortitis, and coronary arteritis have been described.
- This is diagnosed on PCR.
- Treat with doxycycline or IV benzylpenicillin in more severe cases.

Syphilis

- This most commonly produces aortitis; direct involvement of the myocardium is rare.

Protozoal myocarditis

Trypanosoma cruzi (Chagas' disease)

- Found in South America; 20–30% develop cardiac complications.
- Acute infection is usually asymptomatic; however, a small number may experience fever and malaise that can last several weeks. After, most individuals are asymptomatic, but chronically infected.
- Clinical manifestations vary from asymptomatic to progressive cardiac dilatation, with resultant HF. AV conduction defects and ventricular arrhythmias may occur and lead to syncope.
- Echocardiography may show regional motion abnormalities, most commonly inferolateral hypokinesia, dilatation, and LV aneurysms.
- Diagnosis is with the complement fixation test, indirect immunofluorescence, or enzyme-linked immunosorbent assay (ELISA).
- Antiparasitic medication is beneficial in the acute setting, curing 60–80% of cases. There is no role in established cardiomyopathy. Treatment is based on the underlying arrhythmia or severity of HF.

Fungal myocarditis

- Fungal infection is rare and seen in patients who may be immunocompromised due to HIV or are receiving immunosuppressive therapy.

Further reading

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Chapter 6

Pericardial diseases

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Anatomy and function

- The pericardium is a double-walled sac containing the heart and the roots of the great vessels.
- It is composed of a serous visceral layer and a fibrous parietal layer.
- Between these two layers is the pericardial cavity (a potential space), which contains a small amount of pericardial fluid.
- The pericardium acts to anchor the heart to the mediastinum and provides lubrications for movement of the heart.

Aetiology

The pericardium may be involved in a large number of disease processes listed in Box 6.1. In some patients, pericardial disease is the primary disease process dominating the clinical picture, whereas in others, it is a manifestation of a systemic disease. The most common causes include:

- Idiopathic
- Viral
- Uraemic
- Neoplastic
- TB
- Acute MI.

The most likely aetiology will depend on the age, background, and social circumstances of the patient.

Syndromes of pericardial disease

Pericardial reaction to disease processes is limited, and five clinical and pathological forms of pericarditis can be distinguished:

- Acute pericarditis with or without effusion
- Recurrent pericarditis
- Constrictive pericarditis
- Effusive–constrictive pericarditis
- Pericarditis associated with myocardial involvement.

Box 6.1 Causes of pericardial disease

Infections

Viral	Enteroviruses (Coxsackie virus, echovirus), herpesviruses (cytomegalovirus , Epstein–Barr virus, varicella-zoster virus, human herpesvirus 6), parvovirus B19, influenza, human immunodeficiency virus, mumps, rubella
Bacterial	*Mycobacterium tuberculosis*, *Coxiella burnetii*, *Borrelia burgdorferi*, *Staphylococcus*, *Streptococcus*, *Pneumococcus*, *Haemophilus*, *Legionella*
Fungal	*Histoplasma*, *Aspergillus*, *Blastomyces*, *Candida*
Parasitic	*Toxoplasma*, *Echinococcus*

Autoimmune and hypersensitivity diseases

Systemic autoimmune diseases	Systemic lupus erythematosus, scleroderma, dermatomyositis, rheumatoid arthritis
Vasculitides	Eosinophilic granulomatosis with polyangiitis, polyarteritis nodosa, Behçet's disease
Secondary autoimmune disorders	Rheumatic fever, post-myocardial infarction, post-pericardiotomy syndromes
Others	Ankylosing spondylitis, familial Mediterranean fever, inflammatory bowel disease

Pericardial involvement by disease in surrounding organs

Heart	Acute myocardial infarction, myocarditis
Lung	Pulmonary infarction, pneumonia

Neoplastic disease

Primary	Mesothelioma, sarcoma, fibroma, lipoma
Secondary	Lung carcinoma, breast carcinoma, melanoma, lymphoma

Bleeding into the pericardium

Trauma	Penetrating and non-penetrating injuries
Haemorrhagic diathesis	Leukaemia, scurvy
Anticoagulants	Warfarin, DOACs
Other	Dissecting aortic aneurysm

Other causes

Metabolic disorders	Uraemia, dialysis-related, myxoedema, gout
Miscellaneous	Radiation, sarcoidosis, amyloidosis
Drugs	Many drugs can lead to pericardial disease. Examples include: antineoplastic agents, penicillin-based and other antibiotics, amiodarone

Adapted from: Adler Y, *et al*. *Eur Heart J*. 2015;**36**:2921–64.

Acute pericarditis

Aetiology

- Any of the causes listed in Box 6.1 may cause pericarditis. Commonly seen in acute viral pericarditis or post-MI.

Pathology

There is a fibrinous exudate with an inflammatory reaction involving the visceral and parietal pericardium. Epicardial involvement accounts for ECG changes.

Symptoms

- Sharp, stabbing central chest pain is common, with radiation to the shoulders and upper arm.
- Relieved by leaning forward and aggravated by lying down.
- May be accentuated by inspiration, swallowing, or truncal movement.
- Fever, night sweats, and other constitutional symptoms may be present, depending on the aetiology.

Signs

A pericardial friction rub is frequently heard (see Box 6.2).

Box 6.2 A pericardial friction rub

- A superficial, scratchy grating sound
- Best heard in the second to fourth intercostal space with pressure on the diaphragm of the stethoscope
- Position the patient leaning forward, and listen in held inspiration
- Classically triphasic (in >50%, normally at least two components are heard) due to atrial systole, ventricular systole, and rapid ventricular filling

ECG

- The patient is usually in SR, but AF may occur.
- Classical signs are widespread concave ST-segment elevation, ‘saddle-shaped’ (often across multiple arterial territories), and PR segment depression (see Fig. 6.1).
- After a few days, the ST and PR segments return to normal; T waves may become inverted. Q waves do not develop.

Chest X-ray

- The cardiac shadow is not enlarged.

Differential diagnosis

- MI, spontaneous pneumothorax, and pleurisy.

Diagnosis

- Acute pericarditis can be diagnosed based on ≥2 of:
  - Pericardial chest pain
  - Pericardial rub
  - Classical ECG features
  - Pericardial effusion.
- May be supported by pericardial inflammation on imaging (e.g. CMR).

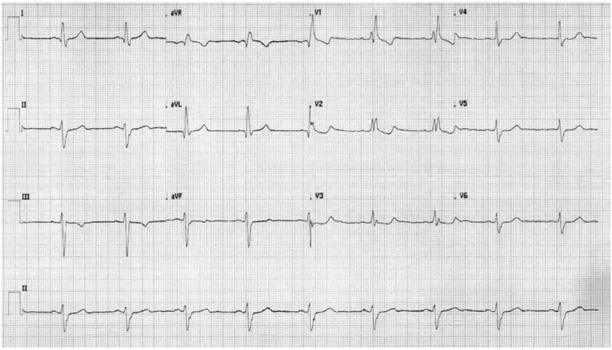

Fig. 6.1 ECG showing sinus tachycardia, with classic saddle-shaped ST-segment elevation across multiple leads, in keeping with pericarditis.

Courtesy © C. Fielder Camm.

Box 6.3 Predictors of poor prognosis* in acute pericarditis

Major:

- Fever >38°C
- Subacute onset
- No response to NSAIDs after >1 week
- Large pericardial effusion/cardiac tamponade

Minor:

- Myopericarditis
- Immunosuppression
- Trauma
- Oral anticoagulant therapy

* Prognostic factors suggest a greater risk of complications, including cardiac tamponade, recurrence, and constriction.

Source: data from Adler Y, *et al. Eur Heart J*. 2015;**36**:2921–64.

Management

- Treat the underlying cause (see subsequent sections in this chapter).
- If no specific aetiology is suspected, and no predictors or poor prognosis are present (see Box 6.3), NSAID treatment can be empirically trialled and the patient may not require admission.
- Colchicine is recommended as a first-line adjunct to NSAID therapy.

Pericardial effusion with or without tamponade

Aetiology

Any of the causes listed in Box 6.1 may cause effusions. Large effusions are common with neoplasia, TB, and uraemic pericarditis.

Common causes of cardiac tamponade

- Pericarditis
- TB
- Trauma
- Neoplastic
- Iatrogenic (invasive procedures, after cardiac surgery)

Reproduced from Adler Y *et al*. *Eur Heart J*. 2015;**36**(42):2921–64, with permission from the ESC. Copyright © The European Society of Cardiology 2015.

Pathology

There is significant fluid exudation with fibrinous inflammation. Fluid may be serous, serosanguineous, haemorrhagic, or purulent, depending on the aetiology. Haemorrhagic fluid suggests TB/neoplasia.

Clinical features

Clinical presentation varies, depending on the rate of fluid accumulation, the amount of fluid, and when the patient is first seen.

Symptoms

Chest pain may be typically pericardial (see ➔ Symptoms, p. 296) or may be dull/heavy due to distension of the pericardium. Dyspnoea is common, and orthopnoea may occur later in the course of the disease. Cough may be present due to compression of surrounding structures. Constitutional symptoms may be present, depending on the cause of the disease.

Signs

Typically, precordial dullness extends beyond the apex beat (which may be impalpable), and dullness is present to the right of the sternum. Dullness and bronchial breathing at the left base posteriorly may be found, due to compression of the left lower lobe bronchus (Ewart's sign). Cardiac tamponade should be considered (see Box 6.4).

ECG

Sinus tachycardia, generalized low-voltage QRS complexes with non-specific ST-segment and T wave changes. QRS electrical alternans suggests a massive pericardial effusion. Total electrical alternans (P–QRS–T) is uncommon and pathognomonic of cardiac tamponade.

Echocardiography

Demonstrates an echo-free zone surrounding the heart. The fluid may not be evenly distributed. Cardiac tamponade is indicated by diastolic collapse of the RV and variation in tricuspid valve inflow (peak E wave velocity drops by ~40% on expiration).

Box 6.4 Clinical features of cardiac tamponade

Beck's triad describes the traditional clinical features of tamponade:
- Hypotension
- Raised jugular venous pressure (JVP)/distended neck veins
- Quiet or absent heart sounds.

The primary defect in cardiac tamponade is interference with diastolic filling of the heart. Other features of cardiac tamponade are:
- Presence of tachycardia
- Pulsus paradoxus (fall in systolic blood pressure on inspiration of >10mmHg or >50% of pulse pressure)—classically by using a sphygmomanometer, but more commonly with an arterial line
- Elevated JVP with brisk 'x' descents and absent 'y' descents
- Rise in JVP on inspiration (Kussmaul's sign)
- Dyspnoea or tachypnoea with clear lungs, and hepatomegaly

Features more common in patients with tuberculous or malignant effusions include:
- Soft tissue density masses
- Thickening of the visceral pericardium
- Presence of fibrinous strands.

The hallmark of a benign, idiopathic effusion is a clear, echo-free space.

Chest X-ray

- Shows a large globular cardiac shadow, usually with clear lung fields.

Cardiac catheterization

Not recommended for routine use in the diagnosis of pericardial disease. While right heart catheterization may help to establish tamponade diagnosis/severity, it is rarely performed. Important findings are:
- Equilibration of mean right atrial, RV end-diastolic, and mean capillary wedge pressure
- Rapid 'x' descent on the right atrial pressure waveform
- Absent 'y' descent on the right atrial pressure waveform
- Pulsus paradoxus.

Management

- When an effusion does not cause haemodynamic impairment and the cause is known (e.g. uraemia), then no further investigations are necessary and treatment consists of treating the underlying cause.
- If the cause is not known, then pericardiocentesis must be considered. Aspiration of the fluid helps to establish the nature of the effusion (see ➔ Pericardial fluid analysis, p. 313).
- Cardiac tamponade is a life-threatening condition—urgent pericardial aspiration is necessary (see ➔ General technique, p. 713). Surgical drainage is indicated for haemopericardium or purulent pericarditis.

Constrictive pericarditis

Aetiology

Globally, constrictive pericarditis is usually due to TB infection, whereas in the UK, it is often idiopathic. Other causes are mediastinal irradiation, purulent pericarditis, previous trauma (surgical or non-surgical) with infection of the pericardial space, and very rarely viral pericarditis.

Pathology

The pericardium becomes a dense mass of fibrous tissue and this may be calcified. This results in encasement of the heart within a non-expansile pericardium.

Symptoms

- Dyspnoea, oedema, and abdominal swelling due to ascites and hepatomegaly.

Signs

Small-volume pulse and pulsus paradoxus. The JVP is elevated, usually very high, with prominent 'x' and 'y' descents. A diastolic knock may be heard at the left sternal border due to the sudden halting of ventricular expansion. The apex beat may be impalpable. Heart sounds are usually soft, with an early third sound coincident with the diastolic knock. The liver is commonly grossly enlarged; ascites is marked, and peripheral oedema is present.

ECG

Abnormal in virtually every case, but changes are non-specific (i.e. generalized low-voltage QRS complexes, and widespread flattening and inversion of T waves). AF is common in the chronic form.

Chest X-ray

A normal/near-normal cardiac size in the presence of marked venous distension or features of HF is suggestive of constrictive pericarditis or RCM. Pericardial calcification with the above findings is diagnostic, but only seen in 5–70% of cases.

Echocardiography

Pericardial thickening may be present. There is a restrictive mitral filling pattern on Doppler, with respiratory variation of >25% over the AV valves (see Box 6.5). Further findings that may differentiate from RCM are detailed in Box 6.7.

Box 6.5 Mayo Clinic criteria for constrictive pericarditis

- Respiration-related ventricular septal shift
- Medial mitral annular e′ velocity ≥9cm/s
- Hepatic vein expiratory diastolic reversal ratio ≥0.79

(Also see Box 6.7.)

Source: data from Welch *et al*. *Circ Cardiovasc Imaging*. 2014;**7**:526–34.

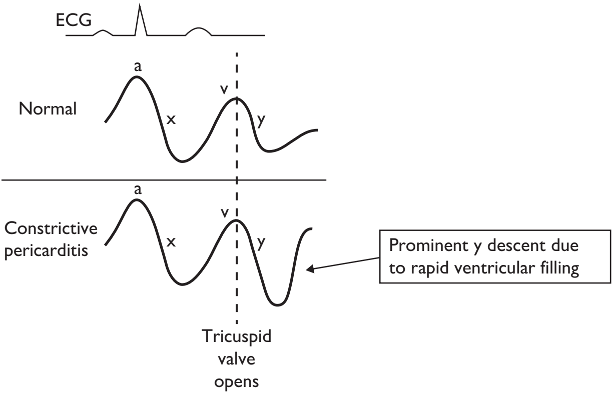
ECG
a
Normal
x
v
y
a
Constrictive pericarditis
x
v
y
Prominent y descent due to rapid ventricular filling
Tricuspid valve opens

Fig. 6.2 Right atrial catheterization findings in constrictive pericarditis.

Computed tomography and magnetic resonance imaging

These demonstrate pericardial thickening (>5mm), and determine the degree and extent of pericardial involvement and calcification.

Cardiac catheterization

Only indicated when non-invasive imaging does not provide a definitive diagnosis. Demonstrates ↑ in, and equalization of, ventricular filling pressures; typically, the difference in RV and LV filling pressures is <6mmHg. The RA waveform shows rapid 'x' and 'y' descents (see Fig. 6.2), and the mean pressure does not ↓ normally with inspiration or may show Kussmaul's sign.

Differential

- RCM, severe TR.

Management

- Constrictive pericarditis is treated by surgical removal of the fibrous constrictive tissue (pericardiectomy).

Effusive–constrictive pericarditis

Aetiology

Characteristically encountered in active TB pericarditis where there are signs of both pericardial effusion or tamponade and constriction. It may also occur in neoplastic, radiation, and septic pericarditis.

Clinical presentation

Symptoms are usually those of constriction. Examination reveals pulsus paradoxus, ↑ JVP with prominent 'x' and 'y' descents. The CXR shows an ↑ cardiac silhouette like that of pericardial effusion.

Diagnosis

The clue to diagnosis is persistent signs of constriction following adequate pericardial drainage.

Management

Treatment of the underlying cause and pericardial drainage are indicated. Pericardiectomy if haemodynamics do not improve.

Recurrent pericarditis

Definition

Defined as a first event of acute pericarditis with a symptom-free interval of ≥4 weeks followed by a further episode of pericarditis. Pericarditis recurs in 15–30% after a single episode of acute pericarditis.

Diagnosis

Diagnosed by using the same criteria as for acute pericarditis.

Management

Treatment of the underlying cause if identified. First-line therapy with NSAIDs/colchicine, and exercise restriction is recommended. Second-line therapy with low-dose corticosteroids can be considered if NSAID/colchicine are contraindicated and an infective cause is excluded.

Myopericarditis

Myocarditis and pericarditis share common underlying aetiologies. The most common cause of myopericarditis is viral infection. Diagnosed as for acute pericarditis, with the addition of elevated markers of myocardial damage (e.g. troponin). Hospitalization is generally suggested. For more details on myocarditis management, see ➲ Myocarditis: management and prognosis, p. 288).

Non-constricted calcific pericardium

This condition is usually discovered during routine radiological examination, which demonstrates pericardial calcification. It is essentially an incidental diagnosis. There are no symptoms and signs of constriction, and the cause is usually unknown.

Viral pericarditis

Clinical presentation

Most patients present with a history of upper respiratory tract infection within the preceding 3 weeks. The viruses most frequently responsible include Coxsackie B virus, echovirus, mumps, influenza, and varicella. Pericardial pain, fever, and malaise are typical. Physical examination reveals a pericardial friction rub and/or characteristic changes of acute pericarditis on ECG.

Course

In most patients, the illness resolves spontaneously in 1–2 weeks. In some patients, the illness recurs on at least one occasion in the next few weeks or months, and in 20% of patients, there are multiple recurrences in the ensuing months or years (benign relapsing pericarditis).

Diagnosis

It is important to search for an underlying disease (see Box 6.1) that may require specific therapy. In most cases of suspected viral pericarditis, routine viral serology is not recommended because of the low diagnostic yield of viral studies and a lack of specific therapy for viral disease. If a definite diagnosis of viral pericarditis is required, identification of viral nucleic acid can be attempted from pericardial fluid samples.

Treatment

- NSAIDs are effective in most patients with viral pericarditis.
- Colchicine is recommended as a first-line adjunct to NSAID therapy (0.5–1mg/day for 3 months); a common side effect is diarrhoea.
- There are no data from randomized controlled trials to guide treatment for relapsing patients who do not respond to NSAIDs and colchicine.
- Corticosteroids (prednisone 0.2–0.5mg/kg for at least 1 month) can be added to NSAIDs and colchicine if incomplete response.
- If patients do not respond adequately, azathioprine (1mg/kg/day), anakinra (an IL-1 receptor antagonist; 1–2mg/kg/day), or intravenous immunoglobulin (IVIg) can be attempted.
- Pericardiectomy is indicated only in frequent and highly symptomatic recurrences that are resistant to medical therapy. However, postpericardiectomy recurrences may occur, possibly due to incomplete resection of the pericardium.

Tuberculous pericarditis

Tuberculous pericarditis is rare in the developed world (accounting for ≤4% of pericardial disease). However, where TB is endemic, it is the primary cause for clinically significant pericardial effusions (50–70%) and is more common in those co-infected with HIV. The disease presents in three forms: pericardial effusion, constrictive pericarditis, and effusive–constrictive pericarditis.

Tuberculous pericardial effusion

- *Pathology:* effusions may occur with or without tamponade. The effusion is bloodstained in >95% of cases and may resemble venous blood. The absence of parenchymal lung disease and presence of hilar lymphadenopathy in many patients suggest a direct spread from lymph node to pericardium.
- *Clinical presentation:* systemic symptoms are variable. Typical pericardial pain and classic ECG features of pericarditis are uncommon. CXR shows an enlarged globular heart, small pleural effusions on one or both sides, and evidence of pulmonary TB in about 30% of cases.
- *Diagnosis:* pericardiocentesis should be performed for a suspected TB pericardial effusion. A definite diagnosis is based on the demonstration of tubercle bacilli in the pericardial fluid or on a histological section of the pericardium. Relevant investigations are detailed in Box 6.6. Pericardial biopsy and drainage offer the advantage of a histological diagnosis and early complete drainage of the pericardium.
- A *probable diagnosis* is made when there is proof of TB elsewhere in a patient with unexplained pericarditis. Acid-fast bacilli (AFB)-positive sputum will only be found in about 10% of cases. Tuberculin skin testing is of little value in endemic and non-endemic areas. A positive enzyme-linked immunospot (ELISPOT) test on pericardial fluid (that detects T cells specific for *Mycobacterium tuberculosis*) is supportive of TB pericarditis.
- *Treatment:* is by means of standard four-drug anti-TB chemotherapy (rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months, then isoniazid and rifampicin for a further 4 months). Although there is no evidence of benefit in TB pericarditis, corticosteroids may be considered in those with HIV-negative TB pericarditis but should be avoided in HIV-positive individuals (↑ HIV-associated cancer).
- *Prognosis:* overall mortality is 17–40%, with HIV-infected individuals having a worse outcome than HIV-negative patients. Repeat pericardiocentesis is required in about 15% of patients. During a 2-year follow-up period, even with correct treatment, 17–40% develop constriction. About 10% of patients will require pericardiectomy.

Tuberculous pericardial constriction

- *Clinical presentation:* most cases have an active inflammatory fibrocaseous tissue surrounding the heart and involving the visceral and parietal pericardium. The clinical presentation is highly variable. Patients may be asymptomatic or have severe signs and symptoms of constriction. Concomitant pulmonary TB is uncommon, and pericardial calcification is found in <5% of cases.

Box 6.6 Investigations for patients with suspected TB pericarditis

Non-pericardial fluid evaluation	
Chest X-ray	To assess for signs of pulmonary tuberculosis (TB)
Echocardiography	Large effusion with fibrinous strands suggestive of an exudate
CT/MRI	Pericardial thickening (>3mm) Mediastinal and bronchial lymphadenopathy (>10mm)
Systemic culture	Culture of sputum, gastric aspirate, and/or urine
Lymph node biopsy	Consider if lymphadenopathy present
Pericardial fluid assessment	
Culture	Direct inoculation into double-strength Kirchner culture medium To identify acid-fast bacilli
Quantitative PCR	Testing for *Mycobacterium tuberculosis* DNA
Exudate/transudate assessment	Fluid and serum protein, serum lactate dehydrogenase
Interferon-γ	>35U/L suggestive of TB diagnosis
Adenosine deaminase	>44pg/mL suggestive of TB diagnosis

- *Treatment:* initial management is with anti-TB therapy. As the process is an active fibrocaseous condition, resolution occurs in 15–20% of patients with medical management over 3–4 months. Pericardiectomy is recommended if no improvement after 6 weeks of treatment or if unsatisfactory improvement after several months. Calcific TB pericarditis is treated by early pericardiectomy and anti-TB therapy.

Effusive–constrictive tuberculous pericarditis

- *Features:* this mixed form is a common presentation of TB pericarditis. There is ↑ pericardial pressure due to effusion in the presence of visceral constriction. Echocardiography shows porridge-like exudation, with loculation of the fluid.
- *Treatment:* standard four-drug therapy. Mortality is ~10%, and ~30% of cases will need pericardiectomy over 2 years of follow-up.

Uraemic pericarditis

- *Pathology:* uraemia produces a fibrinous, often haemorrhagic, inflammation that may lead to tamponade, and constriction in some cases.
- *Management:* symptomatic pericarditis occurring before dialysis initiation will respond to repeated peritoneal dialysis or haemodialysis. Heparin-free dialysis should be used to avoid haemopericardium. Many who develop effusions while on dialysis (dialysis-associated pericarditis) will respond to regime intensification. Non-responders require drainage. Pericardiocentesis is associated with a high risk of intrapericardial haemorrhage.

Neoplastic pericardial disease

Aetiology

Usually secondary to malignancy of the bronchus, breast, or kidney. Primary tumours of the pericardium are rare and usually a result of mesothelioma following asbestos exposure. In those with malignancy, a significant proportion of pericardial effusions are caused by non-malignant disease (e.g. radiation pericarditis, opportunistic infections).

Diagnosis

Metastases may produce a large haemorrhagic effusion or severe constriction when the tumour encases the heart. Malignant cells may be found in 85% of cases of aspirated pericardial fluid. Tumour markers have been used in the diagnosis of malignant effusion.

Management

Depends on the type and stage of malignancy, condition of the patient, and presence of cardiac compression. Commonly, neoplastic pericardial disease is a preterminal event. Pericardiocentesis is effective in relieving cardiac tamponade in the majority of cases. Palliation for recurrent tamponade can be obtained by subxyphoid surgical pericardiotomy (can be performed under local anaesthesia). Alternatively, a percutaneous balloon pericardiotomy can create a pleuro-pericardial window to allow fluid drainage into the pleural space in large effusions in patients with a limited life expectancy. Partial pericardiectomy (pericardial window should be reserved for patients who have a better prognosis and are likely to respond to chemotherapy or radiation).

Intrapericardial instillation of cytostatic/sclerosing agents

These have been used to prevent recurrences of large effusions. Treatment related to the type of tumour indicates that cisplatin may be effective in secondary lung cancer, and thiotepa may be effective in metastatic breast cancer. Tetracycline sclerosis controls malignant effusions in ≤85% of cases, but side effects (e.g. fever, chest pain, atrial arrhythmias, constriction) are common in long-term survivors.

Myxoedematous effusion

Clinical presentation

Effusion with ↑ protein content is common in untreated myxoedema (5–30%). Myxoedema should be excluded in a patient with chronic, asymptomatic pericardial effusion, associated with bradycardia, ↓ QRS complexes, or a history of radiation-induced thyroid dysfunction. Cardiac tamponade is uncommon.

Diagnosis

- Based on serum levels of thyroxine and thyroid-stimulating hormone.

Treatment

- Thyroid hormone replacement results in resolution of the effusion.

Non-tuberculous bacterial (purulent) pericarditis

Background

Purulent pericarditis accounts for <1% of pericarditis cases. More common in those with HIV.

Predisposing conditions

Immunosuppression (e.g. immunosuppressive drugs, lymphoma, HIV/AIDS), pre-existing pericardial effusion, cardiac surgery, and chest trauma. Children—pharyngitis, pneumonia, otitis media, endocarditis, and arthritis.

Precipitating factors

Cardiac surgery, pericardial aspiration, extension of aortic root endocarditis into the pericardial sac, or haematogenous spread from a septic focus such as osteomyelitis or pneumonia.

Causative organisms

- Adults: *Staphylococcus aureus*, *Streptococcus pneumoniae*, Gram-negative bacilli, and anaerobes.
- Children: *Haemophilus*, *S. aureus*, and *Neisseria meningitides*.

Clinical presentation

Presents as an acute, fulminating infectious illness and is fatal if not treated. The most important reason for this poor outlook is failure to suspect the condition in debilitated patients with overwhelming systemic infection.

Diagnosis

Pericardiocentesis shows purulent fluid, with high WCC, low glucose level, positive Gram staining for the organism, and positive pericardial fluid and blood culture.

Treatment

Complete pericardial drainage, preferably through a subxyphoid pericardiotomy with rinsing of the pericardial cavity. Empirical systemic antibiotic therapy should be initiated while awaiting microbiological results. Death is certain if untreated. With correct management, there is a survival rate of up to 85%.

Radiation pericarditis

Aetiology

This usually follows treatment for lymphoma and lung and breast cancer. The incidence of pericarditis depends on how much the heart is included in the field of radiation (e.g. more common following left breast cancer than right breast cancer), and the dose, duration of treatment, and age of the patient.

Pathology

Common cause of effusive–constrictive pericarditis. It may result in myocarditis and premature coronary atherosclerosis.

Timescale

Clinical evidence of pericarditis may occur during or shortly after treatment, but is more usually delayed for ~1 year. Up to 20% of individuals have some pericardial disease within 2 years after chest radiation.

Clinical presentation

The presentation is one of pericarditis with some effusion. In about 50% of cases, there is evidence of tamponade, which requires drainage.

Treatment

Up to 20% of patients will require pericardiectomy because of severe constriction. Operative mortality is high (21%), and post-operative 5-year survival is very low (1%), mostly due to underlying myocardial fibrosis and severe thickening of the visceral pericardium.

Post-pericardiotomy syndrome

Aetiology

Autoimmune inflammatory response to surgical trauma to the pericardium.

Clinical presentation

The syndrome occurs in ~30% of patients undergoing any form of cardiac surgery. It is more common in patients receiving aminocaproic acid during the operation (to control bleeding). The diagnosis is based on at least two of the following:

- Fever without an alternative cause for longer than a week post-operatively
- Pleuritic chest pain
- Friction rub
- Evidence of new or worsening pleural effusion
- Evidence of new or worsening pericardial effusion.

Dry pericarditis or pericarditis with effusion may occur. The illness is generally self-limited and varies in intensity and duration, but usually lasts only 2–4 weeks. The recurrence rate is generally low (<4%).

Prevention

Studies have examined perioperative aspirin, corticosteroids, and colchicine to prevent post-pericardiotomy syndrome. Only colchicine has been shown to have any positive effect, but it also ↑ GI symptoms and is not recommended for prevention.

Treatment

Treatment is the same as for acute pericarditis—namely NSAIDs with adjunct colchicine therapy in the first instance. Anticoagulants should be avoided because of the risk of haemopericardium.

Post-infarction pericarditis

Clinical presentation

Two forms of post-infarction pericarditis may be distinguished:

- The early form of pericarditis occurs within a week. Early pericarditis is rare in those undergoing PPCI (<5%). It is a result of pericardial irritation by adjacent infarcted myocardium.
- Less commonly, a delayed autoimmune reaction may produce pericarditis typically 2–6 weeks after the infarct (Dressler syndrome). The delayed form behaves similarly to post-pericardiotomy syndrome.

Treatment

Aspirin, up to 650mg every 4h for 2–5 days, is recommended as the first-line treatment, with adjunctive colchicine. Occasionally, steroids may be required for relapse but should be avoided as they may delay myocardial healing. Anticoagulants should be avoided because of the risk of haemopericardium.

Traumatic pericarditis

This produces two forms of pericarditis. One is a direct result of trauma with haemorrhage into the pericardial cavity and formation of haemopericardium. If associated myocardial or valvular injury is absent, complete recovery is the rule, although chronic constriction may develop. The second type is a form of recurrent pericarditis allied to the post-pericardiotomy and post-MI syndromes, which may also result in chronic constriction.

Rheumatic fever

This is an important cause of pericarditis, almost invariably associated with severe pancarditis and valvular involvement. Rheumatic pericardial effusion is usually clear, straw-coloured, and sterile. Cardiac tamponade is rare, and the fluid usually resorbs rapidly in response to salicylates or steroid therapy. Chronic constrictive pericarditis is never rheumatic in origin, but an adherent pericardium with flecks of calcification is not uncommon.

Autoimmune pericarditis

Aetiology

Pericarditis may be the presenting feature of SLE, or complicate scleroderma and polyarteritis nodosa.

Clinical presentation

Dry or effusive pericarditis may occur, and it is important to exclude these disorders in patients presenting with idiopathic benign pericarditis. Generally, other signs and symptoms of these diseases will be present.

Granulomatous pericarditis

A complication of rheumatoid arthritis and ankylosing spondylitis, leading to effusion and occasionally constriction. Aortitis and aortic insufficiency may be associated, and occasionally there is invasion of the interventricular septum, producing heart block.

Treatment

Primarily based on dealing with the underlying conditions.

Drugs and toxins

Aetiology

Pericardial reactions to drugs and toxins are rare. Pericarditis may develop as part of the lupus erythematosus-like syndrome (hydralazine, isoniazid, procainamide, methyldopa, reserpine), hypersensitivity reaction (sodium cromoglicate, penicillins, streptomycin), serum sickness, or envenomation (scorpion fish sting).

Management

Consists of removal of the causative agent and symptomatic treatment.

Fungal pericarditis

Aetiology

Fungal pericarditis occurs as a rare opportunistic infection in immunocompromised patients (e.g. immunosuppressive therapy, HIV/AIDS). It is caused by endemic fungi (*Histoplasma*, *Coccidioides*), non-endemic opportunistic fungi (*Candida*, *Aspergillus*, *Blastomyces*), and semifungi (*Nocardia*, *Actinomyces*).

Diagnosis

Fungal pericarditis may resemble TB pericarditis. Fungal staining and culture of aspirated pericardial fluid and pericardial biopsy are necessary to make the distinction.

Treatment

Antifungal treatment with fluconazole, ketoconazole, itraconazole, amphotericin B, or amphotericin B lipid complex is indicated. NSAIDs are used for symptomatic relief. Sulfonamides are the drug of choice for nocardiosis, and a combination of three antibiotics, including penicillin, should be given for actinomycosis.

Amoebic pericarditis

Pathology

Amoebiasis (caused by *Entamoeba histolytica*) occurs mainly in endemic areas and in travellers from these areas (may appear years later). Pericardial complications are rare but carry high mortality, especially with delayed or missed diagnosis. Amoebic pericarditis is usually an extension from an amoebic abscess in the left lobe of the liver.

Clinical presentation

There are two modes of presentation:

- *Hepatic presentation:* an abscess in the proximity of the pericardium, which has not yet ruptured, can cause a pericardial friction rub, a non-purulent pericardial effusion, and ECG and CXR signs of pericarditis.
- *Cardiac presentation:* perforation of the liver abscess into the pericardium results in purulent pericarditis. Onset can be acute, with shock and death, or gradual with tamponade due to the pericardial fluid.

Diagnosis

Should be suspected in patients with purulent pericarditis, signs of cardiac failure, and a tender palpable liver. An ↑ and immobile left hemidiaphragm is suggestive. Definite diagnosis is by pericardiocentesis (typically shows brownish fluid, may simulate anchovy sauce) and serological testing for antibodies resulting from invasive amoebiasis.

Treatment

- *Hepatic presentation:* the pericardial disease resolves with successful treatment of the liver abscess.
- *Cardiac presentation:* pericardial drainage and metronidazole.

Constrictive pericarditis vs restrictive myocardial disease

It is difficult to separate congestive pericarditis from restrictive myocardial disease (see Box 6.7). Pericardiectomy is one of the most satisfying operations in terms of cure.

An *exploratory thoracotomy* is justified if all these tests fail to make a distinction between the two entities.

Box 6.7 Features supportive of constrictive pericarditis vs restrictive cardiomyopathy

	Restrictive cardiomyopathy	Constrictive pericarditis
Clinical findings	• Murmurs of mitral and tricuspid regurgitation	• Pericardial knock
ECG	• Widened QRS complex • Left axis deviation	• Non-specific ST-segment and T wave change
CXR	• No pericardial calcification	• Pericardial calcification
Echocardiography	• Small left ventricle with large atria • ↑ left ventricular (LV) wall thickness • E/A ratio >2 • Short deceleration time • Peak e′ <8.0cm/s	• Respiration-related ventricular septal shift • Pericardial thickening ± calcification • Peak e′ velocity >8cm/s • Respiratory variation in mitral peak E velocity >25%
Cardiac CT	• Normal pericardial thickness (<3mm)	• Pericardial thickness (>3mm) • Pericardial calcification
Cardiac MRI	• Normal pericardial thickness (<3mm) • Myocardial involvement	• Pericardial thickness (>3mm) • Ventricular interdependence
Cardiac catheterization	• Pulmonary artery pressure >50mmHg • LV end-diastolic pressure >5mmHg greater than right ventricular (RV) end-diastolic pressure	• Dip and plateau sign • Equal RV and LV end-diastolic pressures • Ventricular interdependence
Endomyocardial biopsy	• Diagnostic of infiltrative disease • Extensive fibrosis	

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Pericardial fluid analysis

Analyses of pericardial effusion can establish the diagnosis of viral, bacterial, tuberculous, fungal, amoebic, and malignant pericarditis. The appearance of the pericardial fluid should be noted. The tests should be ordered according to the clinical presentation of the patient. However, the following routine samples are useful: (1) biochemistry sample for protein and LDH estimation to distinguish between an exudate and a transudate; (2) microbiology specimen for microscopy, culture, and sensitivity testing; and (3) cytology specimen. The following tests are requested for diagnosis of specific forms of pericarditis:

- *Viral pericarditis:* PCR for cardiotropic viruses.
- *Purulent pericarditis:* Gram staining, at least three cultures of pericardial fluid for aerobes and anaerobes and blood cultures.
- *TB pericarditis:* staining for AFB; bedside inoculation of pericardial fluid into double-strength Kirschner transport medium and culture; adenosine deaminase (ADA) level.
- *Fungal pericarditis:* microscopy and culture.
- *Amoebic pericarditis:* fluorescent antibody test, amoebic enzyme immunoassay.
- *Malignant effusion:* cytology and tumour markers (e.g. carcinoembryonic antigen (CEA)).

In addition, blood tests should be taken for the following:

- *U&Es:* to assess for renal failure as a possible cause.
- *Full blood count*: establish if any features of infection or signs of underlying chronic disease (e.g. anaemia and malignancy).
- *Cardiac biomarkers:* to assess for cardiac damage/myocarditis.
- *Autoimmune screen:* RF, anti-cyclic citrullinated peptide (CCP), ANA, and complement levels if a suspected rheumatological cause.
- *TFTs:* to assess for hypothyroidism.

Further reading

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Chapter 7

Infective endocarditis

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Presentation of endocarditis

Definition

- An infection of the endocardial lining of the heart.
- Endocarditis on permanent pacemaker leads is rare, but recognized.

Key concepts

- Highly variable presentation—depends on intracardiac pathology, virulence of organism, and extracardiac involvement.
- Presentation can be insidious, as in streptococcal infections, or with striking constitutional symptoms as in *Staphylococcus aureus* infection.
- Ask specifically for a history of dental work, infections, surgery, instrumentation, or IV drug use, which may have led to bacteraemia.
- Examine for any potential sources of infection (e.g. teeth/skin lesions).

General manifestations of sepsis

- Includes tachycardia, hypotension, malaise, anorexia, weight loss, fever, rigors, and night sweats. Long-standing infection may result in anaemia, clubbing, and splenomegaly.

Cardiac manifestations of endocarditis

- Valve destruction results in a new or changing murmur. This may result in progressive HF and pulmonary oedema.
- A new harsh pansystolic murmur and acute deterioration may be due to perforation of the interventricular septum or rupture of a sinus of Valsalva aneurysm into the RV.
- AV block (2–4% of infective endocarditis (IE)) cases occur with intracardiac extension of infection into the interventricular septum (e.g. from the aortic valve).
- Intracardiac abscess may occur (25–50% of aortic endocarditis, 1–5% of mitral, but rarely with tricuspid) and is most common in PVE.
- Pericarditis (see ➔ Chapter 6).

Manifestations of immune complex deposition

- *Skin:* petechiae (most common); splinter haemorrhages; Osler's nodes (small, tender nodules (pulp infarcts) on the hands and feet, persisting for hours to days); Janeway lesions (non-tender erythematous and/or haemorrhagic areas on the palms and soles).
- *Eye:* Roth spots (oval retinal haemorrhages with a pale centre located near the optic disc), conjunctival splinter haemorrhages, retinal flame haemorrhages.
- Renal: microscopic haematuria, glomerulonephritis, renal impairment.
- *Cerebral:* toxic encephalopathy.
- *Musculoskeletal:* arthralgia or arthritis.

Table 7.1 Risk factors for infective endocarditis

High risk	Prosthetic valves Previous infective endocarditis Aortic valve disease Mitral regurgitation or mixed mitral disease Cyanotic congenital heart disease Patent ductus arteriosus Uncorrected left-to-right shunt Intracardiac and systemic–pulmonary shunts
Moderate risk	Mitral valve prolapse with regurgitation or valve thickeningIsolated mitral stenosis Tricuspid valve disease Pulmonary stenosis Hypertrophic cardiomyopathy Bicuspid aortic valve disease Degenerative valve disease in the elderly Mural thrombus (e.g. post-infarction)
Low risk	Mitral valve prolapse without regurgitationTricuspid incompetence without structural abnormality Isolated atrial septal defect Surgically corrected left-to-right shunt, with no residual shunt Calcification of mitral valve annulus Ischaemic heart disease and/or previous coronary artery bypass graft Permanent pacemaker Atrial myxoma

Other predisposing factors

- Arterial prostheses or arteriovenous fistulae
- Recurrent bacteraemia (e.g. intravenous drug users, severe periodontal disease, colon carcinoma)
- Conditions predisposing to infections (e.g. diabetes, renal failure, alcoholism, immunosuppression)
- Recent central line.

In many cases, no obvious risk factor is identified.

Complications of endocarditis

Heart failure

- The most common complication of left-sided IE seen in 40–60% of patients.
- Most common when IE affects the aortic valve.
- Mainly caused by new or worsening valvular regurgitation. Intracardiac fistulae may also lead to HF.
- Moderate to severe HF is the strongest predictor of in-hospital and 1-year mortality.

Uncontrolled infection

- Persisting infection is defined as fever and persistent positive blood cultures 7–10 days after initiation of antibiotic therapy.
- May be the result of inadequate antibiotics, resistant organisms, infected lines, systemic embolic events, or locally uncontrolled infection.
- Perivalvular extension (e.g. abscess formation, pseudoaneurysms, fistulae) is the most frequent cause of uncontrolled infection.
- Abscess formation is common in aortic IE (10–40% in native valves, 50–100% in prosthetic valves).
- IV lines should be replaced, and both intracardiac and extracardiac foci of infection should be sought.

Septic emboli

- Septic emboli are seen in 20–50% of patients and may involve any circulation (brain and spleen are most common); PEs with tricuspid endocarditis (see ➔ Right-sided endocarditis, p. 321).
- ~40% of patients who have had an embolic event will have another.
- Risk of emboli is highest in the first 2 weeks of antibiotic therapy.
- Risk depends on several factors:
    - *Organism*: most common with Gram-negative infections, *S. aureus*, or *Candida*
    - *Size of vegetation:* emboli in 30% of patients with no vegetation on echocardiography, 40% with vegetations <5mm, and 65% with vegetations >5mm
    - Mobile vegetations
    - Previous emboli
    - History of diabetes or AF.

Heart rhythm and conduction disturbance

- Conduction disorders are uncommon in IE (risk 1–15%).
- Due to paravalvular extension of IE.
- AV block is mainly associated with left-sided valves.
- AF is seen in around 15% of patients with IE.

Diagnosis of endocarditis

Key facts

- Clinical features can be non-specific, and diagnosis difficult.
- Maintain a high index of suspicion in patients presenting with unexplained fever, a predisposing cardiac lesion, bacteraemia, and embolic phenomena.

Duke classification

- Developed in 1994 as a means of standardizing the diagnosis of IE.
- Highly specific (99%) and sensitive (92%).
- Has undergone several modifications—the most current version is described next.

Major criteria

Blood culture-positive infective endocarditis

- Typical microorganism for IE (see Box 7.1)[1] from two separate blood cultures.
- Persistently positive blood culture (NB blood cultures drawn 12h apart or three or more cultures with the first and last drawn 1h apart).

Single positive blood culture for *Coxiella Burnetii* or phase immunoglobulin G (IgG) antibody titre to *C. Burnetii* >1:800.

Box 7.1 Typical microorganisms for infective endocarditis

• *Staphylococcus aureus*	30%
• Streptococci (including viridans group)	30%
• Coagulase-negative staphylococci	10%
• Enterococci	10%
• HACEK group	2%
• Fungi/yeast	2%
• Multiple organisms	1%
• Culture-negative	10%
• Other	4%

HACEK group: *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* species.

Source: data from Murdoch *et al*. *Arch Intern Med*. 2009;**169**(5):463–73.

Imaging-positive infective endocarditis

- Echocardiogram positive for IE:
  - Oscillating intracardiac mass (vegetation)
  - Abscess, pseudoaneurysm, or intracardiac fistula
  - New partial dehiscence of prosthetic valve
  - Valvular perforation or aneurysm.
- Abnormal activity around the site of a prosthetic valve implant detected by FDG-PET/CT or radiolabelled leucocytes SPECT/CT.
- Definite paravalvular lesions on cardiac CT.

Minor criteria

- Predisposing cardiac condition or injecting drug use.
- Fever >38°C.
- *Vascular phenomena:* arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial and conjunctival haemorrhage, Janeway lesions.
- *Immunological phenomena:* glomerulonephritis, Osler's nodes, Roth spots, RF.
- *Microbiological evidence:* positive blood cultures, but not meeting major criteria, or serological evidence of organism consistent with IE.
- *Echocardiography:* supportive for IE, but not meeting major criteria.
- Embolic events or infectious aneurysms by imaging only.

Diagnosis of infective endocarditis

Pathological criteria

- Microorganisms demonstrated by culture or histology of a vegetation, an embolized vegetation, or an intracardiac abscess specimen.
- Pathological lesions (e.g. vegetation or intracardiac abscess) confirmed by histology showing active endocarditis.

Clinical criteria

- *Definite endocarditis:* two major criteria, or one major and three minor criteria, or five minor criteria.
- *Possible endocarditis:* one major and 1–2 minor criteria, or 3–4 minor criteria.
- *Rejected diagnosis:* firm alternative diagnosis, or sustained resolution of clinical features with <4 days of antibiotic therapy, no evidence of IE at surgery or autopsy, does not meet criteria for possible endocarditis.

Right-sided endocarditis

- Patients most commonly have staphylococcal infection and are unwell, requiring immediate treatment.
- Lesions may be sterilized with IV antibiotics. See Box 7.2 for relative indications for surgical management of right-sided IE.

Box 7.2 Indications for surgical management of right-sided infective endocarditis

- Resistant organisms (*Staphylococcus aureus*, *Pseudomonas*, *Candida*, and infection with multiple organisms)
- ↑ vegetation size despite therapy
- Infections on pacemaker leads (surgical removal of lead and repair, or excision of tricuspid valve)
- Recurrent mycotic emboli

Reference

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Investigation of endocarditis

Laboratory/microbiology investigations

• Blood cultures	Take 3–4 sets of cultures from different sites at least 1h apart, and inoculate a minimum of 10mL/bottle for the optimal pickup rate. Both aerobic and anaerobic bottles must be used. Laboratory should be advised that IE is a possibility, especially if unusual organisms are suspected. In stable patients on antibiotic therapy, doses should be delayed to allow culture on successive days. Ask for prolonged (fungal) cultures in IV drug users
• FBC	May show normochromic, normocytic anaemia, neutrophil leucocytosis, and perhaps thrombocytopenia
• U&Es	May be deranged (should be monitored throughout treatment)
• LFTs	May be deranged, especially with ↑ alkaline phosphatase (ALP) and GGT
• ESR/CRP	Acute phase reaction markers
• Urinalysis	Microscopic haematuria ± proteinuria
• Immunology	Polyclonal elevation in serum immunoglobulins, complement levels
• Swabs	Any potential sites of infection (skin lesions)
• Additional tests	*Aspergillus* precipitins; *Candida* antibodies (rise in titre); Q fever (*C. burnetii*) complement fixation test; *Chlamydia* complement fixation test; *Brucella* agglutinins; *Legionella* antibodies; *Bartonella* species

Core imaging investigations

• CXR	May be normal. Look for pulmonary oedema or multiple infected or infarcted areas from septic emboli (tricuspid endocarditis)
• Echocardiography	TTE may confirm the presence of valve lesions and/or demonstrate vegetations if >2mm in size. TOE is more sensitive for aortic root and mitral leaflet involvement. A normal echocardiography does not exclude IE
• Orthopantomography	All patients should have an orthopantomogram (a panoramic dental X-ray) and a dental opinion

Additional imaging investigations

The following imaging investigations should be considered in patients where the suspicion of IE remains high, but prior investigations have not confirmed the diagnosis.

• CT-PET	^{18}F-FDG-PET/CT may be helpful in the setting of suspected endocarditis on a prosthetic valve (if implanted >3 months). Abnormal activity may be seen around the site of implantation. Should be considered if diagnosis not confirmed with TTE and TOE. Additional utility in suspected device infection
• Cardiac CT	Identification of paravalvular lesions
• Cardiac MRI (used rarely)	Useful in investigation of paravalvular extension, myocardial involvement, aortic root aneurysm, and fistulae
• MRI head	Undertaken to assess for cerebral infectious aneurysms. Should be considered if a patient with IE develops neurological disturbances
• Whole-body CT	To assess for systemic embolic events
• Ventilation/perfusion (V/Q) scan	In cases where right-sided endocarditis is suspected, this may show multiple mismatch defects

Other investigations

• ECG	May have changes associated with any underlying cause. There may be AV block or conduction defects (especially aortic root abscess), and rarely (embolic) acute MI

Antibiotics in endocarditis

Key facts

- Be guided by your local microbiologist, and always follow local antibiotic prescription guidelines.
- Once the diagnosis is confirmed (or suspected), explain to the patient the need for a prolonged parenteral (usually IV) antibiotic course.
- Microbiology will determine sensitivities to, and minimum inhibitory concentration (MIC) of, antibiotics—if the organism is fully sensitive, with 'low' MIC, then shorter courses of antibiotics may suffice.
- Evidence shows that combination therapy is more effective than single chemotherapeutic agents.
- Identification of an organism is invaluable for further management, and three sets of blood cultures should be taken before antibiotics.

Empirical therapy

- Treatment of IE should be initiated if suspected and should not be delayed while awaiting a definitive diagnosis. Often antibiotics need to be started before culture results are available. Be guided by the clinical setting (see Table 7.2).
- Empirical treatment for native valve IE and late PVE should target staphylococci, streptococci, and enterococci.
- Early PVE and healthcare-associated endocarditis should cover MRSA, enterococci, and non-HACEK Gram-negative pathogens.

Table 7.2 Suggested empirical antibiotic regimens

Presentation		Antibiotic	Suggested dose and route
Community-acquired native valve or late prosthetic valve endocarditis	Non-penicillin allergic	Ampicillin	2g 4-hourly IV
		Flucloxacillin	2g 4-hourly IV
		Gentamicin	3mg/kg per day IV
		Ceftriaxone	2g twice daily IV
	Penicillin-allergic	Cefazolin	2g three times daily IV
		Vancomycin	30–60mg/kg per day IV in 2–3 doses
		Gentamicin	3mg/kg per day IV
Early prosthetic valve endocarditis or healthcare-associated endocarditis		Vancomycin	30mg/kg per day IV in 2–3 doses
		Daptomycin	10mg/kg per day IV in one dose
		Gentamicin	3mg/kg per day IV
		Rifampicin	900–1200mg IV in 2–3 doses

Source: data from 2023 ESC guidelines for the management of endocarditis. Delgado *et al*. *Eur Heart J* **44**: 3948–4042.

Specific antibiotic therapy

- Antibiotic therapy should be modified once blood culture results are available.
- This book has not provided antibiotic regimen advice for specific causes of endocarditis, as these are dependent on local guidelines and change significantly over time.
- Individual patients should be discussed with the local microbiology team.

Stopping endocarditis treatment

Duration of treatment

- Controversial—a trend towards shorter courses. Microbiology and infectious diseases opinion is important, especially if resistant and/or uncommon organisms.
- Duration depends on the organism identified, severity of infection, whether it is a native or prosthetic valve, and presence of comorbidities (e.g. renal impairment).
- Inpatient IV therapy is usually recommended for at least 10 days, and total antibiotic therapy for 4–6 weeks.
- Outpatient IV or PO antibiotic therapy can be considered after the first 2 weeks in suitable patients (should have repeat TOE prior to switching).
- The POET trial demonstrated non-inferiority of PO treatment for uncomplicated, stable left-sided IE following an initial 10-day course of IV antibiotics.
- If the patient is well following this period, antibiotic treatment may be stopped. Provided no surgery is indicated (see ➔ Surgery for endocarditis, pp. 332–4), the patient may be discharged and followed up in the outpatient clinic.
- Patients with valvular damage following infection should be followed long term, and patients with VSDs should be considered for closure if haemodynamically compromised.

Monitoring treatment

Patients need careful clinical monitoring both during and for several months after the infection. Reappearance of features suggestive of IE must be investigated thoroughly to rule out recurrent infection or resistance to the treatment regime (see Boxes 7.3 and 7.4).

Box 7.3 Causes for persistent fever in infective endocarditis

- Infection with microorganisms resistant to current antibiotics
- Concomitant infection (e.g. central line, urine, chest, septic emboli)
- Drug allergy (common with penicillin; consider changing/stopping antibiotics for 2–3 days)

Clinical features of progressive endocarditis

- Signs of continued infection, persistent pyrexia, and persistence of systemic symptoms.
- Changes in any cardiac murmurs or signs of HF.
- Development of any new embolic phenomena.
- Inspect venous access sites daily. Change peripheral cannulae every 3–4 days.

Laboratory indices

- Regular (daily) urinalysis.
- Regular U&Es and LFTs.
- Regular CRP.

Box 7.4 Factors associated with relapse

- Inadequate antibiotic therapy (agent, dose, or duration)
- Resistant microorganisms
- Polymicrobial infection in an intravenous drug user
- Empirical therapy for blood-culture-negative infective endocarditis
- Periannular extension
- Prosthetic valve endocarditis
- Abscess formation
- Resistance to conventional antibiotic regimens
- Positive valve culture
- Persistence of fever at 7 days post-operatively
- Chronic dialysis

- FBC—rising Hb and falling WCC suggest successful treatment; watch for β-lactam-associated neutropenia.
- Serum Mg^{2+} (gentamicin-associated hypomagnesaemia).

Microbiology

- Repeated blood cultures (especially if there is continued fever).
- Regular aminoglycoside and vancomycin levels (ensuring the absence of toxic levels and presence of therapeutic levels). Gentamicin ototoxicity may develop with prolonged use, even in the absence of toxic levels.

ECG

- Look specifically for AV block or conduction abnormalities suggesting intracardiac extension of the infection.
- A daily ECG should be performed in all patients.

Echocardiography

- Regular (weekly) TTE may identify clinically silent, but progressive, valve destruction and development of intracardiac abscesses or vegetations.
- The tips of central lines may develop sterile fibrinous ‘fronds’, visible on TOE—change the line and send the tip for culture.
- ‘Vegetations’ need not be due to infection (see ➔ Box 7.6 and Culture-negative endocarditis, pp. 328–9).

Culture-negative endocarditis

- Blood culture-negative IE (BCNIE) is the term used to describe IE when no microorganism is grown by using usual blood culture methods.
- The most common reason for persistently negative blood cultures is prior antibiotic therapy, and up to 30% of patients with IE are affected.
- If clinical response to antibiotics is good, these should generally be continued.

High clinical suspicion of infective endocarditis without positive blood cultures

- In the event that clinical suspicion of IE is high or imaging supports this diagnosis, then further microbiology testing should be considered.
- Blood cultures should be repeated, especially if the patient is febrile. Prolonged culturing should be discussed with microbiology, and special culturing/subculturing techniques considered.
- Systematic serological testing should be undertaken (see Box 7.5). Specific organisms tested for will depend on local epidemiology.
- If serological testing does not reveal a cause, specific PCR assays should be undertaken for *Tropheryma whipplei*, *Bartonella* species, *Candida* species, *Aspergillus* species, and common bacterial species.
- Assays for non-IE should be considered (e.g. ANA (SLE), anticardiolipin antibodies (antiphospholipid syndrome)). In those with porcine bioprostheses, anti-pork antibodies should be tested.
- Histological assessment of excised valvular tissue remains the gold standard investigation. All tissue samples excised during surgery should be collected without fixative or culture medium, and sent to a diagnostic microbiology laboratory.

Box 7.5 Organisms commonly tested for with serology

- *Coxiella burnetii*
- *Bartonella* species
- *Aspergillus* species
- *Mycoplasma pneumoniae*
- *Brucella* species
- *Legionella pneumophila*

Additional strategies

- Consider withholding antibiotics if not already started. This will depend on the clinical context.
- Consider other investigations for pyrexia of unknown origin ('PUO').
- Repeated physical examination for any new signs.
- Regular echocardiography and TOE. 'Vegetations' need not be due to infection (see Box 7.6).

Box 7.6 Causes of 'vegetations' on echocardiography

- Infective endocarditis
- Sterile thrombotic vegetations:
  - Libman–Sacks endocarditis (systemic lupus erythematosus)
  - Primary antiphospholipid syndrome
  - Marantic endocarditis (adenocarcinoma)
- Myxomatous degeneration of valves (commonly mitral)
- Ruptured mitral chordae
- Exuberant rheumatic vegetations (black Africans)
- Thrombus ('pannus') on a prosthetic valve
- A stitch or residual calcium after valve replacement

Common organisms in blood culture-negative infective endocarditis

- *Q fever (C. burnetii):* a ubiquitous infection found commonly in southern France and the Basque region of Spain. *C. burnetii* has a zoonotic reservoir in domestic farm animals (cattle and sheep). Humans are infected by airborne transmission. Q fever is normally a non-specific flu-like febrile illness, with up to 60% of cases being asymptomatic. Endocarditis is a manifestation of chronic infection, which occurs in only a small proportion of those suffering from Q fever (other cardiac manifestations include pericarditis and myocarditis). Serological testing can be undertaken for antibodies to phase 1 antigens, which are present in chronic illness (e.g. endocarditis). Treat with indefinite PO doxycycline ± co-trimoxazole, rifampicin, or quinolone. Treatment success is defined as an anti-phase 1 antibody title of <1:200.
- *Brucellosis:* caused by an intracellular proteobacteria; *Brucella* infection occurs through consumption of unpasteurized animal milk and cheese. Organisms may take up to 8 weeks to grow. Serological testing usually confirms the diagnosis. Treatment is primarily with doxycycline + co-trimoxazole + rifampicin. Treatment success is defined by an antibody titre of <1:60.
- *Chlamydia psittaci:* a rare cause of endocarditis with a zoonotic reservoir in feral and domesticated birds. Commonly, there is a history of exposure to birds and there may be associated atypical pneumonia. Diagnosis is confirmed by using complement fixation tests to detect raised antibody titres.
- *Fungi:* fungal infections are most commonly seen in prosthetic valve IE, IV drug users, and immunosuppressed patients. *Candida* is the most common species and may be cultured. Detection of antibodies may be helpful, although levels may be raised in normal individuals. Detection of a rising titre is of more use. Other fungal infections (e.g. aspergillosis) are rare but may be diagnosed with serology. Mortality is >50%. Bulky vegetations are common. Treatment is with amphotericin B ± flucytosine. Prosthetic valves must be removed.

Prosthetic valve endocarditis

Key facts

- Devastating complication—frequently needs reoperative surgery (see Box 7.7).
- 1–6% of patients with prosthetic valves and accounts for 10–30% of all IE cases.
- Conventionally divided into early (<1 year post-operatively) and late (>1 year post-operatively) due to differences in agents of infection between these time points.

Box 7.7 Factors associated with poor outcome in prosthetic valve endocarditis

- Older age
- Diabetes mellitus
- Healthcare-associated infection
- Staphylococcal/fungal infections
- Early prosthetic valve endocarditis
- Heart failure
- Stroke
- Intracardiac abscess

Investigations

- TOE is mandatory in suspected PVE; however, diagnostic yield is lower than in native valves.
- A negative echocardiogram does not rule out PVE.
- A new periprosthetic leak is a major criterion and should trigger further imaging (e.g. cardiac CT or nuclear).

Early prosthetic valve endocarditis

- *Incidence:* <1%.
- *Causes:* most commonly due to staphylococci, Gram-negative bacilli, diphtheroids, or fungi. Generally, infection has begun in the perioperative period.
- *Risks:* prior endocarditis, prolonged hospital stay.
- *Infection site:* infection usually occurs at the junction between the annulus and the sewing ring, leading to dehiscence, fistulae, and perivalvular abscess.
- *Clinical features:* often a highly destructive, fulminant infection, with paravalvular leak, valve dehiscence, abscess formation, and rapid haemodynamic deterioration.
- *Treatment:* discuss with the surgeons early. Patients commonly require reoperation. Mortality is high (45–75%).

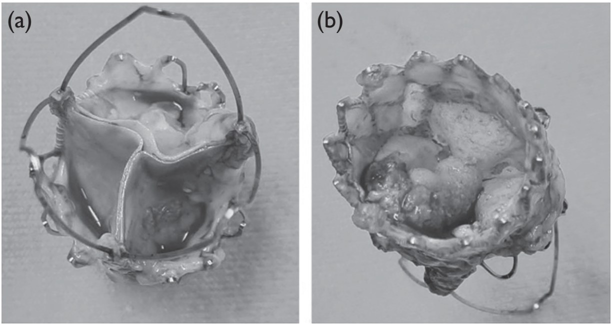

Fig. 7.1 A TAVI valve with vegetation viewed from aortic (a) and ventricular (b) views.

Reproduced from Gurevitz C *et al*. *Eur Heart J Case Reports* 2022;**6**(8):ytac302, with permission of the European Society of Cardiology.

Late prosthetic valve endocarditis

- *Causes:* the pathogenesis is different to that of early PVE—two mechanisms:
  - Abnormal flow around the prosthetic valve ring produces microthrombi and non-bacterial thrombotic vegetations (NBTVs), which may be infected during transient bacteraemia. The source is commonly dental or urological sepsis, or from indwelling venous lines.
  - Early infection with indolent organism (e.g. *Streptococcus epidemidis*) that takes several months to manifest clinically.
- *Common organisms:* same as those for native valve IE.
- *Risks:* invasive procedures, dental sepsis—as for primary endocarditis.
- *Treatment:* frequently needs surgical intervention, and this carries high mortality, but less than for early PVE. It may be possible to sterilize infections on bioprostheses with IV antibiotics only. Surgery (see ➔ Surgery for endocarditis, pp. 332–4) may then be deferred.

Surgery for endocarditis

Discuss early with the regional cardiothoracic centre—immediate intervention may be appropriate.

- Surgical intervention may be necessary, either during active infection or later, because of the degree of valve destruction. Surgical intervention is required in about half of patients with IE.
- Surgery during the acute phase of IE is associated with significant risk.
- Optimal timing depends on a number of factors:
  - Haemodynamic tolerance of the lesion
  - Presence of complications
  - Infection features.
- The choice of antimicrobial therapy should be modified, depending on microbiological results from intraoperative specimens. Samples should be sent for culture, staining, immunological testing, and PCR.
- Antimicrobial treatment duration is dependent on the clinical picture:
  - *Culture-negative operative specimens:* complete the current course of antibiotics
  - *Culture-positive operative specimens:* start a further 6-week course of antibiotics based on culture sensitivities.
- In patients with intracranial haemorrhage, surgery should be delayed for 28 days. In those with embolic stroke, surgery should not be delayed as long as there is no coma and haemorrhage has been excluded by CT or MRI of the head.

Haemodynamic tolerance

- If the patient is haemodynamically stable, surgery may be delayed until the antibiotic course is completed. Final management depends on the valve affected, the degree of destruction, and its effect on ventricular function. Severe AR and MR usually require surgery.
- Decompensation (severe CCF or low CO syndrome with functional renal failure) is an indication for urgent/emergency surgery, but mortality is high.
- 'Metastable' patients who have been successfully treated after an episode of acute decompensation should be considered for early operation after 2–3 weeks' antibiotic therapy.

Complications of infective endocarditis which may indicate early surgery

- High-degree AV block.
- Perforation of interventricular septum.
- Rupture of sinus of Valsalva aneurysm into the RV.
- Intracardiac abscess.
- Prosthetic endocarditis, especially associated with an unstable prosthesis.

Right-sided infective endocarditis

- TR, if well tolerated, is managed medically. See Box 7.2 for surgical indications.

Infection features which may affect surgical timing

- Persistence or relapse of infection (clinical and laboratory indices), despite appropriate antibiotics, may be due to either a resistant organism or an abscess (paravalvular, extracardiac). Consider valve replacement if no extracardiac focus is found.
- The organism may influence the decision—consider early surgery for fungal endocarditis or prosthetic endocarditis with *Escherichia coli* or *S. aureus*.

Surgical options

- The two objectives of surgery in IE are to remove infected material and to reconstruct cardiac structures (see Table 7.3).
- Intraoperative assessment of the valve after surgical debridement is important to determine the optimum surgical technique.
- Additional risk of operative mortality associated with endocarditis is 2–5%, with significant further risk if the patient presents in cardiogenic shock or after prolonged hospital stay.

Table 7.3 Indications and timing of surgery in left-sided native valve infective endocarditis

Recommendations: indications for surgery	Timing[a]
A. Heart failure	
Aortic or mitral IE with severe acute regurgitation, obstruction, or fistula causing refractory pulmonary oedema or cardiogenic shock	Emergency
Aortic or mitral IE with severe acute regurgitation or valve obstruction causing symptoms of heart failure or echocardiographic signs of poor haemodynamic tolerance (early mitral closure or pulmonary hypertension)	Urgent
B. Uncontrolled infection	
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent
Persisting fever and positive blood cultures (>7–10 days) despite appropriate antibiotic therapy	Urgent
Infection caused by fungi or multiresistant organisms	Urgent/ non-urgent
Prosthetic valve endocarditis caused by staphylococci or non-HACEK Gram-negative bacteria	Urgent/ non-urgent
C. Prevention of embolism	
Aortic or mitral IE with large vegetations (>10mm) following one or more embolic episodes despite appropriate antibiotic therapy	Urgent
Aortic or mitral IE with large vegetations (>10mm) and other indications for surgery	Urgent

[a] Emergency surgery: surgery performed within 24h; urgent surgery: within a few days; non-urgent surgery: after at least 1 or 2 weeks of antibiotic therapy.

Surgery may be preferred if a procedure preserving the native valve is feasible.

Source: data from Delgado *et al*. *Eur Heart J*. 2023;**44**:3948–4042.

Mitral/tricuspid valve disease

- In mitral and tricuspid endocarditis without significant destruction, valve repair (rather than replacement) is the best solution. This minimizes prosthetic material, maximizing freedom from reoperation.
- Single leaflet damage can be repaired with an autologous or bovine pericardial patch.
- Ruptured chordae can be replaced with polytetrafluoroethylene neochordae.
- Mitral valve repair can be achieved in 80% of patients if undertaken by experienced teams.

Aortic valve disease

- Replacement of the valve using biological or mechanical prosthesis is the gold standard.
- Aortic valve repair can be achieved in experienced centres in around a third of patients.
- It is suggested that homografts may reduce persistent or recurrent infection risk and should be favoured over mechanical prostheses.
- The presence of an annular abscess may require root replacement.

Post-operative complications

- Severe coagulopathy requiring clotting factors.
- Bleeding or tamponade requiring chest re-exploration.
- Acute kidney injury requiring haemodialysis.
- Stroke.
- Low CO syndrome.
- Hospital-acquired pneumonia.
- AV block following aortic root abscess resection (preoperative LBBB on ECG predicts the need for post-operative pacemaker insertion).

Endocarditis prophylaxis—dental

Rationale

- Dental procedures are thought to cause transient bacteraemia, which may allow bacteria to attach onto the endocardium.

Guideline recommendations

- The 2015 ESC guidelines on IE suggest that antibiotic prophylaxis should be considered only for those at highest risk.
- In contrast, the NICE guidelines (2008) on IE suggest that antibiotic cover for dental procedures is not recommended.

Key facts

- Low-grade bacteraemia occurs regularly during the day due to brushing teeth, flossing, or chewing.
- Most evidence in humans has not shown a link between dental procedures and incident IE.
- The ESC has maintained recommendations to give antibiotic prophylaxis to those at highest risk (see Box 7.8), as there is remaining uncertainty regarding the risk of IE following dental procedures. In those at high risk, the prognosis for IE is worse, and the number of patients at high risk is small, mitigating concern about potential harm at a population level due to antibiotic prophylaxis.

Procedures in which prophylaxis is recommended

- Procedures involving manipulation of the gingival or periapical region of the teeth (see Table 7.4).
- Perforation of the oral mucosa.

Procedures in which prophylaxis is not recommended

- Local anaesthetic injections in non-infected tissues.
- Treatment of superficial caries.
- Removal of sutures.
- Dental X-rays.
- Placements/adjustment of prosthodontic or orthodontic appliances.
- Trauma to the lips or oral mucosa.

Box 7.8 Conditions where antibiotic prophylaxis is recommended

- Prosthetic valves, including transcatheter valves
- Where prosthetic material was used for cardiac valve repair
- Previous infective endocarditis
- Cyanotic congenital heart disease
- Ventricular assist devices
- Congenital heart disease repaired with prosthetic material (for 6 months, lifelong if residual shunt or valvular regurgitation)

Source: data from Delgado *et al*. *Eur Heart J*. 2023;**44**:3948–4042.

Endocarditis prophylaxis—non-dental

Respiratory tract procedures

- Antibiotic prophylaxis is not recommended for respiratory tract procedures, including bronchoscopy or laryngoscopy, and transnasal or endotracheal intubation.

Gastrointestinal and genitourinary procedures

- Antibiotic prophylaxis is not recommended for gastroscopy, colonoscopy, cystoscopy, or TOE.

Dermatological and musculoskeletal procedures

- Antibiotic prophylaxis is not recommended for any procedure.

Body piercing and tattooing

- Case reports of IE after body piercing exist, especially following tongue piercing in high-risk patients.
- However, no convincing data exist regarding the rate of IE following these procedures in high-risk patients.
- Antibiotic prophylaxis is not recommended.
- Patients should be informed about the risks; those at high risk or with a prosthetic valve should be strongly advised against piercings or tattooing.
- All patients at ↑ risk of IE should be given general advice on reducing risk (see Box 7.9).

Table 7.4 Antibiotic prophylaxis

	Single dose, 30–60mi prior to procedure
No penicillin allergy	Amoxicillin 2g PO
Allergy to penicillin	Doxycycline 100mg PO

Box 7.9 Infective endocarditis prevention measures that should be advised in high- and intermediate-risk patients

- Strict dental and cutaneous hygiene
- Dental review 6-monthly if high risk (annually in others)
- Disinfection of wounds and strict cutaneous hygiene
- Eradication/↓ chronic bacterial carriage (e.g. skin, urine)
- No self-medication with antibiotics
- Strict infection control measures for all at-risk procedures
- Discourage piercing and tattooing
- Limit infusion catheters/invasive procedures when possible
- Strict adherence to care bundles for central/peripheral cannulae

Source: data from Delgado *et al. Eur Heart J*. 2023;**44**:3948–4042.

Outpatient review

Be very wary about discharging patients from routine follow-up.

General considerations

- Risk of IE recurrence between 2% and 6%.
- VHD tends to worsen with time. Consequently, long-term follow-up is the norm rather than the exception.
- Very minor lesions (e.g. mild MR, AR, or TR) with no symptoms are relatively benign and may not need regular review.
- Follow-up should be by the endocarditis team or a heart valve specialist where available.

Relapse vs reinfection

- *Relapse:* a repeat episode of IE caused by the same microorganism.
- *Reinfection:* an episode of IE caused by a new infecting agent.
    - Reinfection may occur with the same bacterial species.
    - Recurrence by the same species <6 months suggests relapse, and later suggests reinfection.
    - See Box 7.3 for factors associated with relapse.
    - Patients with reinfection are at higher risk of death/need for valve replacement.

Symptoms review

- Has there been any progression since the last review? (NB can be insidious and patients often do not notice—ask about specific activities and whether they can still do them as well as before)
- Are there any new symptoms (particularly chest pain, dyspnoea, palpitations, and syncope)?
- Are there any symptoms to suggest endocarditis (fevers, weight loss, malaise, joint, or back pains)?
- When did they last visit the dentist, and are they aware of the need for prophylaxis?
- Ask about medications. (What are they on? Have there been any additions or dose changes? If so, why?)
- Review anticoagulation and antiplatelet therapy—is there an indication? Is compliance adequate?

Examination

Look for peripheral stigmata of endocarditis (see ➔ Manifestations of immune complex deposition, p. 316). Record the rate and character of the pulse and BP. Assess the JVP and apex beat, and then auscultate the precordium—remember to listen to the lung bases and to check for pedal oedema.

Investigations

- Always review current ECG, TTE (± CXR), and compare with previous results to look for progression of the condition.
- FBC and CRP should be measured at the initial clinic visit and afterwards, as dictated by clinical suspicion.
- Consider Hb/haematocrit and LDH in patients with a prosthetic valve.

Specific conditions

With all conditions, patients should be advised to seek earlier review if symptoms change in the intervening period.

- *MS:* if mild, with no symptoms, can be reviewed every 2 years. If moderate to severe (or with symptoms), should be seen at least annually.
- *MR:* patients with asymptomatic mild MR can be reassured and discharged. If moderate to severe MR or with symptoms, should be seen at least annually. If LV dimensions start to enlarge or EF declines, consider referral for surgery.
- *AS:* asymptomatic patients with mild AS should be seen every 2–3 years. Anything more severe than moderate AS or with symptoms should be seen annually. Mild AS: echocardiography every 3–5 years; moderate AS: every 1–2 years. In severe AS or patients with moderate AS and symptoms, workup for AVR should be commenced.
- *AR*: asymptomatic patients with mild AR can be reassured and discharged. Patients with symptoms or moderate AR should be seen at least annually. If the LV starts to dilate or severe AR, refer for consideration of AVR.
- *Prosthetic valves:* see annually (↑ incidence of valve failure after 5 years). If new valvular dysfunction is detected, then investigate promptly (often requiring admission), as this can dramatically worsen very rapidly. Once regurgitation is detected, close follow-up with two-dimensional and Doppler echocardiography every 3–6 months is indicated.

Chapter 8

Adult congenital heart disease

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Introduction

- CHD is one of the most common congenital defects, occurring in ~0.8% of newborns.
- Advances in therapy have led to a dramatic improvement in outcome, such that over 80% of infants, even with those with complex CHD, are expected to reach adolescence and early adulthood.
- As a result of the successes of paediatric cardiology and surgery, *there are now more adults than children with CHD*. In addition, there are patients with structural or valvular CHD who may present late during adulthood.
- It is estimated that there are 13 million individuals with CHD worldwide, and the majority have had palliative/reparative, rather than corrective, surgery. Therefore, many will need further cardiac operations.

Role of specialist congenital heart disease centres

- Initial assessment and continuing care of adults with known or suspected CHD.
- Surgical and non-surgical interventions.
- Advice and ongoing support for non-cardiac surgery and pregnancy.
- Training new specialists and providing evidence-based clinical decision-making.
- In the UK, adult CHD (ACHD) care is based around a hub-and-spoke model, with centres arranged into three levels:
  - *Level 1:* specialist ACHD surgical centres
  - *Level 2:* specialist ACHD centres
  - *Level 3:* local ACHD centres.
- All patients should be seen at least once in a specialist centre. Ongoing care locations are likely to depend on condition complexity (see Box 8.1), but care decisions must be individualized.

Transition from paediatric to adult care

> *No patient with CHD should reach adulthood without a clear management plan.*

- A smooth transition from the paediatric to the ACHD specialist is essential. This should be tailored to the individual patient, with in-built flexibility.
- Ideally, a specialist transition clinic should be set up, with input from both adult and paediatric teams. Transfer to the adult unit may occur at age 16–18 years, with the process starting at age 12–14 years.
- Patient education about the diagnosis and specific health behaviour, including contraception/pregnancy planning, should be included. Patient passports that include detailed diagrams of the individual cardiac defect and relevant information on topics such as exercise and need for antibiotic prophylaxis should be prepared for each patient.
- Treat ACHD with respect. The patients may often know more about their condition and its management than the 'emergency' medical team they consult; be patient and listen.
- Patients are often accompanied by (a) parent/s into the second or third decade. They can prove a great source of information and help. Increasingly in the UK, ACHD physicians are available for advice, either via email or by telephone. None will refuse a call for help. *Get to know your local specialist centre!*

Box 8.1 Disease complexity and hierarchy of care for the adult with congenital heart disease

Classification	Examples	Likely care setting
Severe	Any cyanotic heart disease, Eisenmenger syndrome, Fontan repairs, transposition of the great arteries, valvular atresia	Exclusive care by specialist unit
Moderate	Coarctation of the aorta, Marfan's syndrome, moderate/large atrial septal defect (ASD), repaired transposition of the great arteries, tetralogy of Fallot	Shared care between local and specialist centre
Mild	Mild pulmonary valve stenosis, postoperative ASD/ventricular septal defect	Ongoing management in local centre

Further resources on adult congenital heart disease:

1. Baumgartner H, De Backer J, Babu-Narayan SV, *et al*. 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J*. 2021;**42**(6):563–645. doi:10.1093/eurheartj/ ehaa554.

2. Stout KK, Daniels CJ, Aboulhosn JA, *et al*. 2018 AHA/ACC guideline for management of adults with congenital heart disease. *Circulation*. 2019;**139**(14):e698–800.

Congenital heart disease in adults

Acyanotic lesions

- ASD (see ➔ Acyanotic defects: septal defects, pp. 352–4)
- VSD (see ➔ Ventricular septal defect, pp. 353–4)
- Atrioventricular septal defect (AVSD) (see ➔ Atrioventricular septal defect, p. 354)
- PDA (see ➔ Patent ductus arteriosus, p. 360)
- Pulmonary stenosis (PS) (see ➔ Pulmonary stenosis, p. 222)
- Left ventricular outflow tract (LVOT) obstruction (see ➔ Acyanotic defects: left ventricular outflow tract obstruction, pp. 362–3)
- CoA (see ➔ Acyanotic defects: coarctation of the aorta, pp. 356–7)
- Anomalous pulmonary venous drainage (see ➔ Anomalous pulmonary venous drainage, pp. 360–1)
- Anomalous coronary arteries (see ➔ Anomalous coronary arteries, pp. 358–9)
- Ebstein's anomaly (see ➔ Cyanotic defects: Ebstein's anomaly, p. 370)

Cyanotic lesions

- Transposition of the great arteries (TGA) (see ➔ Cyanotic defects: transposition of the great arteries, pp. 364–5)
- Tetralogy of Fallot (ToF) (see ➔ Cyanotic defects: tetralogy of Fallot, pp. 366–7)
- Fontan patients (see ➔ Cyanotic defects: Fontan circulation, pp. 368–9)
- Congenitally corrected TGA (ccTGA) (see ➔ Congenitally corrected transposition of the great arteries, pp. 364–5
- Severe Ebstein's anomaly (see ➔ Cyanotic defects: Ebstein's anomaly, p. 370)

Terminology in CHD

- Sequential segmental analysis offers a step-by-step approach to systematically describe simple to complex congenital defects, based on their morphological characteristics.
- The three segments of the heart for sequential segmental analysis are the atria, ventricles, and arterial trunks.

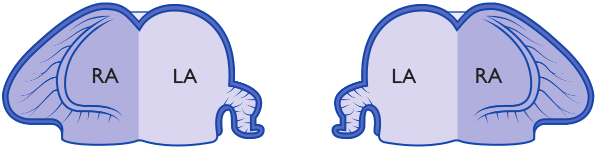
Sequential segmental analysis

Atria

- First identify the atrial appendage arrangement (see Fig. 8.1).
- *Morphological RA:* broad base and prominent pectinate muscles.
- *Morphological LA:* narrow, hook-shaped, and smooth.
- *Situs solitus:* the usual arrangement.
- *Situs inversus:* a mirror-image arrangement.
- *Isomerism:* duplication of either the LA or the RA (see Fig. 8.1).
- *RA isomerism:* associated with asplenia.
- *LA isomerism:* associated with polysplenia.
- *Great vessels:* may provide information on atrial arrangement. Normally, the abdominal aorta is on the left of the spine, and the inferior vena cava (IVC) on the right. This is reversed in a mirror-image arrangement. If they both occur on the same side of the spine, this indicates right isomerism. In left isomerism, blood from the lower part of the body drains into the azygos vein. The enlarged vein will be ipsilateral and posterior to the aorta.

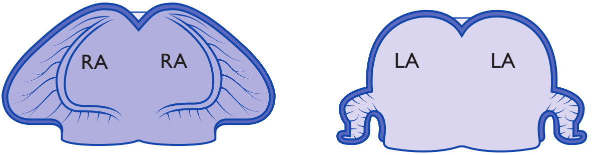
Ventricles

- *RV:* coarse apical trabeculations and a moderator band. The tricuspid valve (TV) septal leaflet attaches to the septum.
- *LV:* has fewer trabeculations by comparison. The MV attaches to the papillary muscles.



Usual

Mirror-imaged



Isomerism of right atrial appendages

Isomerism of left atrial appendages

Fig. 8.1 Atrial arrangement (as labelled).

Atrioventricular connections

- *Concordant connections:* where the LA connects to the LV and the RA connects to the RV.
- *Discordant connections:* where the LA connects to the RV and the RA connects to the LV (see Fig. 8.2).
- *Ambiguous connections:* AV connections in the case of isomerism.
- In the case of a univentricular heart, possibilities include a double-inlet ventricle, absent right and absent left AV connections (Fig. 8.3), with a dominant LV and an incomplete RV or a dominant RV and an incomplete LV or a single indeterminate ventricle.

Arterial trunks

- *Ventriculo-arterial (VA) concordance:* a normal relationship between the ventricles to the aorta and PA.
- *VA discordance:* the aorta arises from the RV, and the PA from the LV (as in TGA and ccTGA).
- *Double outlet:* both arterial trunks are connected to one ventricle (indeterminate, left, or right).

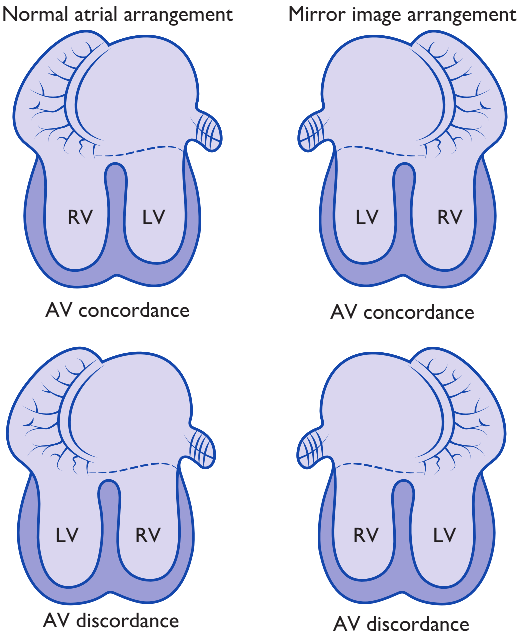

Normal atrial arrangement
Mirror image arrangement
RV
LV
LV
RV
AV concordance
AV concordance
LV
RV
RV
LV
AV discordance
AV discordance

Fig. 8.2 Atrioventricular connections.

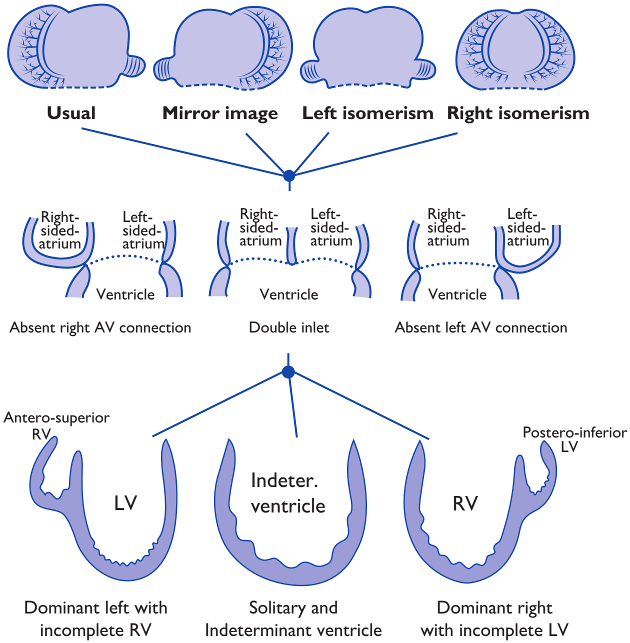

Usual
Mirror image
Left isomerism
Right isomerism
Right-sided-atrium
Left-sided-atrium
Ventricle
Absent right AV connection
Right-sided-atrium
Left-sided-atrium
Ventricle
Double inlet
Right-sided-atrium
Left-sided-atrium
Ventricle
Absent left AV connection
Antero-superior RV
LV
Dominant left with incomplete RV
Indeter. ventricle
Solitary and Indeterminant ventricle
Postero-inferior LV
RV
Dominant right with incomplete LV

Fig. 8.3 Univentricular atrioventricular connections.

Cardiac position

- The heart is normally in a left-sided position within the thorax (*levocardia*), in contrast to *dextrocardia* (right-sided) and *mesocardia* (central).

Additional diagnostic terminology

- *Atresia:* congenital absence or imperforate orifice, valve, or vessel.
- *Conotruncus:* refers to the conus (myocardial segment between the ventricles and the outflow semilunar valves) and truncus, which is the fibrous segment between the outflow valves (aortic and pulmonary) and the aortic sac, giving rise to the great arteries.
- *Major aortopulmonary collateral arteries (MAPCAs):* systemic to pulmonary vessels that arise to supply oxygenated blood to the lungs when the native pulmonary circulation is underdeveloped. Usually in association with cyanotic conditions such as complex pulmonary atresia or ToF subtypes.

Assessment of patients with CHD (1)

History

- Family history of CHD.
- Exposure to teratogens/toxins during pregnancy.
- CHD suspected during pregnancy or at birth (it may be helpful to ask a carer, parent, or relative in some cases).
- History of prolonged childhood illnesses.
- Prior interventions:
  - Any catheter- or surgical-based interventions
  - Names of previous paediatric cardiologists and surgeons, as well as the unit where surgery, if any, was performed.
- Dental hygiene.
- Smoking/drug and alcohol intake.

Current symptoms

- *Shortness of breath:* ask if this is at rest/on exertion. Ask about the ability to climb stairs and walk on the flat/hills, and the distance they can cover. Particularly ask about breathlessness on lying down.
- *Chest pain:* consider the onset, character, radiation, duration, precipitating/relieving factors, and any associated symptoms.
- *Syncopal episodes:* ask about precipitating event, associated symptoms, and duration of loss of consciousness.
- *Palpitations:* ask about onset, duration, frequency, and associated symptoms. Ask the patient to tap out the rate and rhythm of palpitations.

General inspection

- Chart the patient's height, weight, BP (always in the arm opposite the thoracotomy scar), and oxygen saturations.
- Examine for dysmorphic features related to a genetic syndrome associated with CHD (see ➔ Genetic syndromes associated with CHD, pp. 380–1).
- Does the patient appear anaemic, jaundiced, or cyanosed?

Infective endocarditis

- *Peripheral features:* splinter haemorrhages, Osler node, Janeway lesions, or Roth's spots.
- *Risk factors:* poor oral hygiene, dental caries, infected gums, tattoos, or body piercing.

Specific signs in patients with CHD

Inspection

Cyanosis

- Oxygen saturation should always be measured by pulse oximetry.
- *Central cyanosis:* indication of arterial desaturation. Present when the level of deoxygenated Hb is >5g/dL. Thus, it is dependent, in part, on Hb concentration. May be absent in an anaemic patient with significant desaturation.
- *Differential cyanosis:* cyanosis of the lower extremities, with mild/no cyanosis of the upper extremities. Deoxygenated blood from the pulmonary trunk entering the aorta distal to the left subclavian artery (e.g. non-restrictive PDA with pulmonary vascular disease and right-to-left shunt).

Clubbing

- Bulbous enlargement of the nails, with loss of the nail fold angle.
- Cardiac causes include cyanotic CHD and IE.

Previous operation scars?

- Lift the patient's arms and look for evidence of thoracotomy scars.

Scars and cardiac surgery

- *Right posterolateral thoracotomy*: Blalock–Taussig (BT) shunt.
- *Left posterolateral thoracotomy:* central or BT shunt, PDA ligation, surgical repair of coarctation of the aorta (CoA).
- *Median sternotomy:* commonest access approach for a wide range of cardiac pathologies and surgeries.
- Minimally invasive surgery includes alternative access routes (e.g. mini-sternotomy, sub-mammary, and axillary incisions).

Jugular venous pressure

- *Exaggerated 'a' wave:* results from ↑ resistance to atrial filling, may occur in isolated severe PS or tricuspid atresia.
- *'Cannon' waves:* episodic very large 'a' waves. Occur in heart block when the atrium contracts against a closed TV.
- *Prominent 'v' wave:* is characteristic of TR.

Palpation

- Feel all the pulses, including the femorals.
- Assess for radiofemoral delay in CoA.
- *Bounding pulses:* characteristic of severe AR or PDA.
- *Weak/absent radial pulse:* common in ipsilateral (classical) BT shunt.
- *Coanda effect:* an ↑ in the right brachial pulse due to supravalvular stenosis in patients with Williams' syndrome. Turbulent flow in the stenotic aortic region adheres to the vessel wall, creating selective streaming of blood into the innominate artery.
- *Thrills:* may be felt in the femoral vessels, reflecting AV malformation following prior cardiac catheterization.
- *Differential BPs:* check in the upper and lower limbs. In lower limbs, inflate the cuff around the calf and palpate the posterior tibial artery.

- *Apex beat:* is the apex beat displaced or even in the right chest?
- *Abdominal organs:* check the liver and stomach are correctly positioned.
- *Situs inversus with the apex in the right chest:* the mirror image of normal; 95% of patients with mirror-image dextrocardia have no coexisting congenital cardiac disease.
- *Situs solitus with the apex in the right chest:* invariably associated with CHD, and is often complex and unpredictable.
- *Parasternal heave:* represents RV overactivity, most marked when there is both pressure and volume overload of the chamber.
- *Palpable second heart sound (HS2):* detected in the upper left intercostal space (ICS) when PHT is present.

Systematic approach to auscultation of a patient with congenital heart disease

1. Listen to the heart sounds

First heart sound

- As mitral closure is loudest, the first heart sound (HS1) is best heard at the apex.
- Loud HS1: heard in MS or sometimes with an ASD.
- Soft HS1: feature of ↓ myocardial contractility or long PR interval.

Second heart sound

- *Fixed splitting*: occurs in the presence of a significant ASD; is best appreciated in the high or mid-left sternal border.
- HS2 is accentuated in the presence of PHT.
- HS2 is widely split following repair of ToF.

2. Check for systolic/diastolic murmurs

(Draw an imaginary line between the nipples.)

Murmurs that are loudest above the nipple line

- Generally ESMs.
- A ‘to and fro’ murmur at the upper left sternal edge after cardiac surgery suggests RVOT obstruction and PR.
- Arise from the RVOT/LVOT (if carotid or suprasternal thrill—suggests it is from the LVOT).
- *Ejection clicks:* if heard, the murmur is valvular in origin. The ejection click of AS is best heard at the apex.
- *Turbulence across a coarctation repair:* ESM, best heard in the interscapular region and associated with a left thoracotomy.

Murmurs that are loudest below the nipple line

- Generally pansystolic and arise from MR/TR or from a VSD.
- *MVP:* a mid-systolic click and systolic murmur, best heard with the patient standing up.
- *Continuous murmur:* arises from an arterial duct, a systemic-to-pulmonary shunt, or AV fistulae.

Assessment of patients with CHD (2)

ECG

- An ECG should be performed at every clinical attendance.
- Look for atrial/ventricular hypertrophy and the presence of BBB.
- *ATs:* are especially common after all forms of atrial surgery (e.g. intra-atrial repair for TGA). If AT is suspected, record a 12-lead ECG during administration of IV adenosine.
- *AFl:* consider if there is a constant rate of 100 or 150bpm—easily confused with 'SR' or sinus tachycardia.
- Measure the QRS duration in all post-operative ToFs: >180ms ↑ risk of arrhythmia, RV dilatation, and SCD.

Chest X-ray

- Identification of right-to-left orientation; assess cardiac/visceral positions.
- Bronchial branching permits diagnosis of isomeric cardiac defects (e.g. symmetrical morphological right bronchi in RA isomerism).
- Record the cardiothoracic ratio in the notes (see Fig. 8.4).
- Rib notching related to collateral blood supply in severe CoA.
- Assess pulmonary vasculature (see Box 8.2).

Blood work

- Baseline blood work (may vary across centres) includes FBC, creatinine, serum uric acid, clotting, and BNP/NT-proBNP.
- *Iron studies:* if clinical concern regarding ↓ iron. Should include serum ferritin, iron, transferrin, and transferrin saturation.
- *Folic acid/vitamin B12:* if ↑ mean corpuscular volume (MCV) or normal MCV and ↓ ferritin.
- Cyanotic patients with elevated haematocrit of >55% will require citrate-adjusted collection tubes for clotting profile analysis.

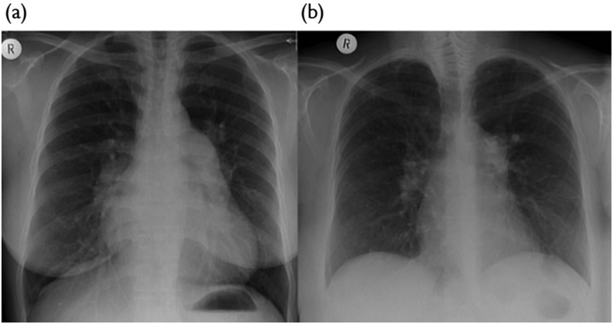


Fig. 8.4 (a) Chest X-ray of a patient with an atrial septal defect (ASD), illustrating cardiomegaly with right heart dilatation, dilated pulmonary artery, and plethoric lung fields. (b) Chest X-ray of a patient with ASD and Eisenmenger syndrome with ↓ vascularity/'pruning' of the peripheral lung fields.

Box 8.2 Pulmonary vasculature in patients with congenital heart disease

Vascularity	*Associated conditions*
↑	• Left-to-right shunt (ASD, VSD) • Pulmonary oedema • Obstructed pulmonary venous drainage
↓	• RVOT obstruction (e.g. isolated severe PS, following ToF repair) • Pulmonary hypertension
Unilateral ↑	• Overperfused major pulmonary collateral artery • Obstructed pulmonary venous drainage (e.g. after Mustard/Senning repair for TGA)

ASD, atrial septal defect; VSD, ventricular septal defect; RVOT, right ventricular outflow tract; PS, pulmonary stenosis; ToF, tetralogy of Fallot; TGA, transposition of the great arteries.

Role of cardiopulmonary exercise testing

- Assessment of function and fitness; distinguishes from limitations due to lack of aerobic fitness.
- Evaluate HR (and exercise-induced arrhythmias) and BP response.
- Monitoring SaO_2 to improve risk stratification in cyanosed patients.
- Comparison of upper vs lower limb BP following coarctation repair.
- Role in pregnancy counselling and planning.
- Serial CPET should be incorporated as part of follow-up to aid in decision-making for surgical or catheter-based interventions.

Imaging modalities in congenital heart disease

Echocardiography

- First-line investigation in CHD directed by history and examination.
- Provides anatomical, morphological, and functional data.
- Should be performed with a standardized sequential approach by an experienced examiner with detailed knowledge of CHD.

Cardiac magnetic resonance

- A superior imaging modality for extracardiac pulmonary arterial and venous vasculature, RV volumes and function, valvular pathology (e.g. PR), and tissue characterization (e.g. fibrosis, scar, fat).

Cardiac computed tomography

- Growing role in assessing for coronary anomalies and collaterals, evaluating intra- and extracardiac masses and parenchymal lung disease.
- Cumulative ionizing radiation exposure should be considered.

Cardiac catheterization

- Performed for specific anatomical or physiological assessment and/or to obtain accurate haemodynamic data (e.g. quantifying shunts and pulmonary vascular resistance (PVR), or identifying collaterals).
- Performed as part of percutaneous transcatheter procedures (e.g. ASD, PFO, or PDA closure).
- Required in patients being considered for cardiac transplantation.
- An ageing ACHD population will need angiography for diagnosis or treatment of CAD or as a pre-surgical workup.

Acyanotic defects: septal defects

Atrial septal defect

Epidemiology

- One of the commonest lesions; occurs in ~1 in 1500 individuals.
- May remain undiagnosed until adult life.

Pathophysiology

- Secundum defects located in the middle septum are most frequent (80%), followed by primum defects located near the crux (15%).
- Less common variants include sinus venosus defects located near the SVC/IVC (5%) and unroofed coronary sinus defects where LA separation is partially/completely missing (<1%).

Associated anomalies

- *Secundum defects:* may be associated with Holt–Oram syndrome or upper limb deformities.
- *Superior sinus venosus defects:* often associated with anomalous drainage of the right pulmonary veins to the SVC/RA.
- Other associations include persistent left SVC, PS, and MVP.

Clinical features

- Patients may remain asymptomatic until adulthood when they may present with exertional dyspnoea and supraventricular arrhythmias (new-onset AFl or AF).
- Key signs include fixed splitting of HS2 (can be difficult to appreciate clinically) and a systolic pulmonary flow murmur.

Investigations

- *ECG:* often demonstrates incomplete RBBB and right axis deviation (RAD).
- *CXR:* right heart/PA dilatation, ↑ pulmonary vascularity.
- *Echocardiography:* RV volume overload, shunt quantification.
- *TOE:* secundum and sinus venosus defects require better characterization of defect size and surrounding rims, and, in the latter case, specific evaluation of pulmonary venous connections.
- *CMR:* may be useful if echocardiography is insufficient.
- *Cardiac catheterization:* to assess PVR in cases with ↑ PA pressures.

Management

- *Patients with significant shunt:* signs of RV overload, Qp/Qs >1.5, and PVR <5 Wood units (WU). Should generally undergo closure, regardless of symptoms. Shunting ↑ with age as the LV stiffens, and therefore, the outcome is best when the lesion is repaired at age <25 years.
- ASDs of all sizes in patients with paradoxical emboli (with exclusion of other causes) should be considered for closure.
- Most secundum defects are amenable to transcatheter closure (Class I) (see ➲ Percutaneous transcatheter interventions for CHD, pp. 378–9). Antiplatelet therapy is required for at least 6 months.
- All other ASDs, such as sinus venosus defect and partial AVSD, require surgical closure, although transcatheter redirection for sinus venosus defects is an emerging technique.

- NB in patients with impaired LV or significant MR, ASD closure may worsen HF due to resultant ↑ in filling pressure. These patients may require balloon occlusion of the defect, with haemodynamic assessment prior to closure.

Follow-up

- Duration and frequency are centre-specific, generally:
  - Those repaired at age <25 years without residual haemodynamic issues may not require regular follow-up.
  - If a residual shunt, ↑ PA pressures, arrhythmias, or repair at age >40 years, the patient should have regular follow-up, with timing determined on an individual basis.

Ventricular septal defect

Epidemiology

- Second commonest CHD at birth (30–40% of infants with CHD). Most are small.

Pathophysiology

- Most frequently occurs in the perimembranous region (80%).
- Less commonly in the muscular/trabeculum (15–20%), and outlet (5%) or inlet defects as part of an AVSD.
- Spontaneous closure occurs mainly in muscular and perimembranous VSDs.

Associated anomalies

- VSDs are often seen in complex CHD (e.g. TGA, ToF, ccTGA) (see ➔ Cyanotic defects: transposition of the great arteries, pp. 364–5; ➔ Cyanotic defects: tetralogy of Fallot, pp. 366–7; ➔ Cyanotic defects: transposition of the great arteries, pp. 364–5).

Clinical features

- Often asymptomatic in adulthood if small with minimal left-to-right shunt, or if repaired in childhood with no/minimal residual defect.
- May present with dyspnoea and cyanosis in Eisenmenger syndrome with PHT (pulmonary vascular disease associated with reverse right-to-left shunting via intracardiac communication).
- A harsh pansystolic murmur may be heard if the VSD is small.
- Late-onset complications include LV volume overload and HF, risk of IE, double-chamber RV, and progressive AR due to aortic valve prolapse in outlet VSDs.

Investigations

- *ECG:* normal (small VSDs), RBBB common in post-surgically repaired VSD patients (due to ventriculotomy).
- *Echocardiography:* quantification of location and number of defects, shunt direction, LV overload, pulmonary pressure assessment, AR.
- *CMR:* may be useful if echocardiography is insufficient.
- *Cardiac catheterization:* in cases of ↑ PA pressures to assess PVR.

Management

- VSDs should be closed if asymptomatic, with evidence of LV volume overload, previous IE, and progressive AR. In patients with PHT with PVR of 3–5WU, VSD closure should be considered when there is still a significant left-to-right shunt (Qp:Qs >1.5). VSDs may be amenable to surgical or transcatheter closure.

Follow-up

- Following device closure, patients should have regular follow-up for the first 2 years, then 2- to 5-yearly if stable.
- Interval 24h ECG recordings should be considered due to the long-term risk of CHB.

Atrioventricular septal defect

Epidemiology

- Accounts for 3% of CHD, can be partial or complete.
- Common defect in patients with Down syndrome (>75%).

Pathophysiology

- Characterized by a common AV annulus bordered by ≤5 leaflets.
- *Partial:* central fusion of anterior and posterior bridging leaflets. Creates separate right and left AV valves with an atrial-level shunt.
- *Complete:* shunting at interatrial and interventricular levels.

Associated anomalies

- Seen in patients with ToF and isomeric syndromes.

Clinical features

- Clinical presentation will depend on the size of the ASD/VSD and whether the left-sided AV valve is competent.
- Shortness of breath at rest and on exercise; symptoms of arrhythmias and cyanosis may be present.

Investigations

- *Echocardiography:* assessment of the AVSD, AV valves, ventricular function, and PAP.
- *CMR:* may be useful if echocardiography is insufficient.
- *Cardiac catheterization:* in cases of ↑ PAP to assess PVR.

Management

- Intervention is via surgical means in patients with significant RV volume overload, symptomatic patients with moderate to severe AV valve regurgitation, and asymptomatic patients with severe AV valve regurgitation and LV end-systolic diameter (LVESD) ≥45mm and/or LVEF ≤60%.

Follow-up

- Following surgical repair, patients should be seen every 2–3 years. If there are residual abnormalities, this may need to be more frequent.

> Intervention is not recommended for septal defects in patients with Eisenmenger physiology.

Acyanotic defects: coarcation of the aorta

Epidemiology

- Five to 8% of CHDs, with a prevalence of ~3/10,000 live births.

Pathophysiology

- Occurs as discrete stenosis, usually just beyond the origin of the left subclavian artery where the ductus arteriosus inserts or as a long, hypoplastic segment of the aorta.

Associated anomalies

- Bicuspid aortic valve.
- MV stenosis (parachute MV—Shone syndrome).
- LVOTO at valvular, supravalvular, or subvalvular levels.
- Associated with Williams' syndrome, Turner syndrome (in ♀ patients) (see ➔ Genetic syndromes associated with CHD, pp. 380–1), congenital rubella, or Takayasu aortitis.

Clinical features

- Most patients seen in adult clinics will have already undergone surgery and may be asymptomatic. Clinical features below describe unrepaired CoA.
- Patients may present with headache, dizziness, shortness of breath, claudication, and abdominal angina.
- Some may present for the first time with systemic hypertension. Always feel the femoral pulses! During follow-up, right arm and lower limb BPs should be recorded.
- Key clinical features include upper limb systolic hypertension with BP gradient >20mmHg between upper and lower limbs in significant coarctation, radiofemoral delay, suprasternal thrill, vascular murmur at the back, and continuous murmurs secondary to collaterals.

Investigations

- *ECG:* possible LVH.
- *CXR:* rib notching due to collaterals, dilated or ectatic ascending aorta, 'figure 3' sign due to double contouring of the descending aorta and dilated left subclavian artery.
- *Echocardiography:* site and severity of coarctation. Doppler gradients are unreliable, whereas a CW Doppler 'diastolic tail' is highly suggestive of significant coarctation (see Fig. 8.5).
- *CMR and CT:* serial imaging should be undertaken to evaluate the whole aorta to delineate coarctation anatomy, collaterals, and complications (e.g. aneurysms, restenosis, or residual coarctation).
- *Cardiac catheterization:* gold standard for assessment of coarctation severity.

Management

- Repair of CoA or re-coarctation is indicated when patients are hypertensive, with ↑ gradient between the upper and lower limbs (≥20mmHg).

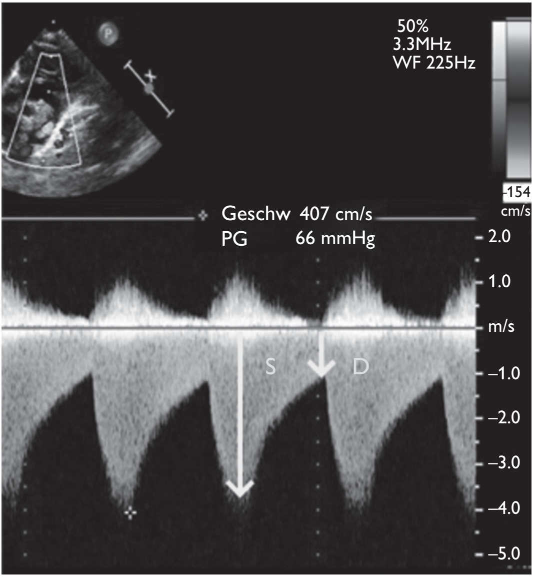


Fig. 8.5 Continuous wave Doppler.

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- *Transcatheter balloon dilatation and stenting:* constitutes first-line treatment for adult patients with native coarctation and suitable anatomy, thus avoiding the risks of thoracic aortic surgery.
- *Surgical repair:* techniques include end-to-end anastomoses, subclavian flap aortoplasty, interposition of a tube graft, patchy aortoplasty, and ascending to descending aorta bypass grafts.

Follow-up

- Lifelong surveillance is necessary to rule out aneurysm formation or recurrence.
- *Long-term sequelae:* potentially include systemic hypertension, re-coarctation, residual coarctation, aneurysm formation, and associated risk of rupture. Re-coarctation should be suspected if there are reduced femoral pulses or a radiofemoral delay on examination.

Acyanotic defects: congenital anomalies of the coronary arteries

Epidemiology

- Anomalous coronary arteries (ACAs) refer to the origin of a coronary artery from an ectopic position from the aorta.
- Occurs in <1% of the population.
- Commonest is separate origins of the LAD and left circumflex (LCx) arteries (0.41% incidence) or the LCx arising from the RCA (0.37% incidence).
- Classified based on their pathways (see Box 8.3).

Pathophysiology

- Anatomical high-risk features of the ACA include a slit-like ostium, an acute take-off angle, and an interarterial or intramural course, in addition to proximal narrowing or an elliptical vessel.

Clinical features

- Can be asymptomatic.
- Presentation with chest pain, dyspnoea, palpitations, syncope (due to myocardial ischaemia), or SCD.

Investigations

- *ECG:* often normal, rarely shows ischaemic changes or arrhythmia.
- *Echocardiography:* may demonstrate ACA calibre, ostium, proximal course, and relationship to RVOT. Myocardial RWMAs may be present if there is underlying ischaemia.
- *CMR and CT:* allow anatomical delineation.
- *Stress testing:* stress echocardiography, myocardial perfusion testing, and stress perfusion CMR (with physical stress) may reveal ischaemia or tachyarrhythmias. The absence of ischaemia should not be viewed as reassuring.
- *Coronary angiography and IVUS*: characterizes vessel calibre and the presence of obstruction via dynamic imaging.

Prognosis

- Poorer outcomes with anomalous left coronary artery (LCA) from the pulmonary artery (ALCAPA).
- The LCA arising from the right sinus is more likely to be malignant than the RCA arising from the left sinus.

Box 8.3 Classification of congenital coronary artery anomalies

- *Anomalies of origin* (e.g. anomalous left coronary artery from the pulmonary artery (ALCAPA)
- *Anomalies of course:* myocardial bridging
- *Anomalies of termination:* coronary artery fistula

Box 8.4 Indications for intervention in those with congenital coronary artery anomalies

- All patients with ALCAPA
- Symptomatic patients with anomalous right coronary artery from the pulmonary artery (ARCAPA)
- Anomalous aortic origin of the coronary artery and typical angina, with evidence of stress-induced ischaemia in a matching territory or high-risk anatomy
- Asymptomatic patients, with evidence of ischaemia or with high-risk anatomy alone

Management

- Intervention should be considered, based on a number of factors (see Box 8.4).
- Definitive management for high-risk patients is surgical intervention.
- Depending on the specific anatomy, surgical repair strategies include unroofing, patch ostioplasty, reimplantation of the anomalous vessel, or PA translocation. Standard coronary artery bypass techniques may also be employed (rarely).

Acyanotic defects: patent ductus arteriosus and anomalous pulmonary venous drainage

Patent ductus arteriosus

Epidemiology

- Found in 0.3–0.8% of term infants, but commoner in preterm neonates (20–60%) in whom PDAs typically close over time without therapy.

Pathophysiology

- Persistent communication between the proximal left PA and descending aorta, distal to the left subclavian artery. The left-to-right shunt produces LV volume overload, which can evolve to PHT, with Eisenmenger physiology with large PDAs.

Clinical features

- Clinical presentation will depend on the size of the PDA.
- Patients may be asymptomatic or present with symptoms and signs of LV or RV failure, depending on whether LV volume overload or PHT is the predominant feature.
- Patients with Eisenmenger demonstrate differential cyanosis (lower limbs cyanotic).

Investigations

- *Echocardiography:* assessment of PDA, degree of LV volume overload, and PAP.
- *CMR:* may be useful if echocardiography is insufficient.
- *Cardiac catheterization:* in cases of ↑ PAP to assess PVR.

Management

- PDA closure is recommended in patients with evidence of LV volume overload and in those with PAH and PVR 3–5WU, with significant right-to-left shunting (Qp/Qs >1.5).
- Transcatheter device closure is preferred when technically feasible.
- Surgery is undertaken when the duct is too large for device closure or if aneurysm formation means transcatheter closure is unsuitable.

Follow-up

- Patients with no residual shunt, normal LV, and normal PAP do not require follow-up after 6 months.
- Those with residual PAH should be followed up every 1–3 years.

Anomalous pulmonary venous drainage

Epidemiology

- Rare, with partial anomalous pulmonary venous drainage (PAPVD) reported in 0.7% at autopsy. Total anomalous pulmonary venous drainage (TAPVD) is even less common.

Partial anomalous pulmonary venous drainage

Pathophysiology

- Occurs when an abnormal connection between a pulmonary and a systemic vein results in right heart volume overload. The commonest form of PAPVD is an anomalous right upper pulmonary vein to the SVC, which is usually associated with a sinus venosus ASD.

Associated conditions

- Other abnormal connections include drainage of the right pulmonary vein(s) to the IVC, with right lung hypoplasia (known as Scimitar syndrome), or left upper pulmonary vein(s) to the left innominate vein.
- Eighty per cent associated with ASD. Also seen with conotruncal defects and isomeric syndromes.

Clinical features

- May be asymptomatic, noted to have incidental systolic murmur (flow murmur from shunt or due to associated lesions).
- Exertional dyspnoea or palpitations.
- Recurrent chest infections in Scimitar syndrome with pulmonary sequestration.

Investigations

- *Echocardiography:* assess for RV volume overload and PAP. TTE often limited direct visualization of PAPVD. TOE provides visualization of entire interatrial septum and pulmonary venous connections.
- *CMR and CT:* optimal evaluation of pulmonary venous drainage; CMR allows shunt quantification.

Management

- Indications follow the principles of those for closure of ASD (see ➔ Acyanotic defects: septal defects, pp. 352–4).

Total anomalous pulmonary venous drainage

Pathophysiology

Congenital abnormality in which all pulmonary veins drain to the RA. There are four anatomical subtypes:

- Supracardiac: pulmonary venous confluence drains to the brachiocephalic vein, SVC, or azygos vein via the vertical vein
- Infracardiac: pulmonary venous return below the diaphragm via hepatic veins or IVC
- Intracardiac: pulmonary veins drain directly to the RA or via the coronary sinus.
- Mixed: variations of the other three subtypes, in which each lung often has separate pulmonary venous drainage.

Clinical features and management

- Neonates may present with cyanosis and HF requiring urgent surgery.
- TAPVD with pulmonary venous obstruction is a surgical emergency.
- Adults will almost universally have undergone surgical repair.

Acyanotic defects: left ventricular outflow tract obstruction

- May occur at valvular, subvalvular, or supravalvular levels, either in isolation or in combination. Lifelong follow-up is required.

Valvular aortic stenosis

Epidemiology

- Bicuspid aortic valve is the commonest cause of congenital AS, with a prevalence of 1–2% in the general population.

Associated conditions

- Thirty per cent of individuals with BAV have an associated aortic or cardiac abnormality, including CoA, interrupted aortic arch, VSD, and parachute MV.
- It is often associated with ascending aortic dilatation, which confers a risk of aneurysm, rupture, and dissection.

Clinical features

- Patients often remain asymptomatic for years, with regular surveillance required to monitor progression.
- Individuals may present with symptoms of outflow tract obstruction (angina, syncope, exertional dyspnoea).

Investigations

- *Echocardiography:* to assess AS severity and LVEF. Consider low-dose dobutamine stress to diagnose low-flow/low-gradient AS.
- *Exercise testing:* in asymptomatic patients to evaluate exercise tolerance, BP response, and arrhythmias for risk stratification.
- *CT/MRI:* for aortic assessment/quantification of valve calcification.

Management

- Surgery should be considered in symptomatic patients, asymptomatic patients with severe AS if they develop symptoms during exercise testing, any patients with severe AS and LV dysfunction (EF <50%), or if undergoing other cardiac surgery.
- May occasionally be amenable to balloon valvuloplasty in young adults with non-calcified valves, but more commonly requires surgical intervention.
- Aortic valve replacement (bioprosthetic, mechanical, or homograft) or Ross operation (see ➔ Ross operation, p. 377), no anticoagulation, but potential need for further interventions, critically operator-dependent) can be offered.

Supravalvular aortic stenosis

Epidemiology

- Accounts for 8–30% of all congenital LVOTO pathologies.

Pathophysiology

- Characterized by elastin arteriopathy that most commonly results in an external hourglass deformity, with luminal narrowing of the ascending aorta.

Associated conditions

- Frequently associated with Williams' syndrome (see ➔ Genetic syndromes associated with CHD, pp. 380–1) or familial homozygous hypercholesterolaemia.
- May be associated with multiple stenoses in the origins of the coronary arteries and the aortic arch arterial branches.

Clinical features

- Patients usually present with symptoms of outflow tract obstruction, with chest pain, dyspnoea, or syncope.

Investigations

- See ➔ Valvular aortic stenosis, p. 362.

Management

- Surgery should be undertaken in symptomatic patients with mean Doppler gradient of ≥40mmHg or in patients with a mean Doppler gradient of <40mmHg with symptoms of LVOTO or LV systolic dysfunction (LVEF <50%), or when surgery is already required.

Subvalvular aortic stenosis

Epidemiology

- Least common obstructive lesion of the LVOT, accounting for ~8%.

Pathophysiology

- Subaortic stenosis is uncommon, caused by a fibrous ridge in the LVOT or fibromuscular narrowing.

Associated conditions

- It can occur in isolation or in association with ASD, VSD, or Shone complex.

Clinical features

- Patients usually present with symptoms of outflow tract obstruction.

Management

- Surgery is indicated in symptomatic patients with mean Doppler gradient of ≥40mmHg or severe AR, asymptomatic patients with a mean Doppler gradient of <40mmHg but with LVEF <50%, Doppler gradient of ≥40mmHg with marked LVH, and Doppler gradient of ≥40mmHg with a fall in BP on exercise.
- Surgery involves either circumferential resection of the fibrous ring or Konno procedure of aortic annular enlargement for fibromuscular/tunnel-type subaortic stenosis.

Cyanotic defects: transposition of the great arteries

Cyanosis is due to bidirectional or right-to-left shunting caused by a connection between the systemic and pulmonary circulation.

Transposition of the great arteries

Epidemiology

- This accounts for ~5% of CHD; ♂:♀ = 2:1.

Pathophysiology

- The aorta arises from the RV, and the PA from the LV due to VA discordance.
- Without mixing (e.g. via VSD or PDA), this is uniformly lethal.

Clinical features

- Post-operatively, ↓ exercise capacity (c.f. to the general population).
- *Palpitations:* may occur due to atrial/ventricular arrhythmias.
- *Features of RV failure (systemic ventricle):* ↑ with longer follow-up.
- *Signs of venous congestion:* suggests baffle obstruction.
- *Ejection/pansystolic murmur:* outflow obstruction/TR, respectively.

Investigations

- *ECG:* possible findings include RVH and AFl/AF.
- *Echocardiography:* assessment of LV and RV, TR, PAH, leakage/obstruction of atrial baffles, and pulmonary venous return.
- *CMR:* may be useful for RV assessment and atrial baffle assessment.
- *CPET:* unmasks baffle leaks which may be asymptomatic at rest with desaturation, evaluation of arrhythmias.
- *Holter monitoring:* evaluation of arrhythmias.
- *Cardiac catheterization:* in cases of ↑ PAP to assess PVR.

Management

- *Intra-atrial repair:* most adult survivors had a Mustard/Senning procedure (see ➲ Surgical operations for CHD, pp. 374–7). Produced excellent early survival, but significant late morbidity/mortality.
- *Arterial switch:* procedure developed in the 1980s (➲ Surgical operations for CHD, pp. 374–7); these patients now in middle adulthood.
- May present with complications after switch procedures (see Box 8.5).

Follow-up

- Annual follow-up for patients with atrial switch-corrected TGA.

Congenitally corrected transposition of the great arteries

Epidemiology

- This is an uncommon condition (<1% of CHD).

Pathophysiology

- Double discordant anatomy (AV and VA).
- Systemic venous return enters via the SVC and IVC to the RA, with blood flowing into the subpulmonary LV before entering the PA.
- Oxygenated blood returns via the pulmonary veins to the LA, which flows into the systemic RV before being ejected through the aorta.

Clinical features

- Symptoms are dependent on associated malformations.

- *Cyanosis:* if VSD and PS/pulmonary vascular disease also present.
- *RV failure:* often asymptomatic but may have features of RV failure.
- *Palpitations:* secondary to SVT may also occur in later life.

Investigations

- *ECG:* ↑ PR/CHB, Q waves in leads II/III/aVF/V1–V3 (right-to-left septal activation).
- *Echocardiography:* demonstrates double discordance, associated abnormalities, AV valve regurgitation.
- *CMR:* may be useful for RV assessment and shunt quantification.
- *Holter monitoring:* evaluation of arrhythmias, higher-grade AV block (ongoing risk of CHB of ~2% per annum).
- *Cardiac catheterization:* in cases of ↑ PAP to assess PVR.

Management

- *Corrective surgery:* double switch (atrial and arterial, Rastelli–Senning) operation in children (see ➔ Surgical operations for CHD, pp. 374–7), not recommended in adults.
- *Valve replacement:* should be performed in severe AV valve regurgitation before systemic ventricular EF <40%.
- *Pacing:* may be required for AV block. Suggestion that biventricular pacing may help to preserve RV function, compared with lone LV pacing.

Follow-up

- Patients with ccTGA should be followed up annually.

Box 8.5 Complications following atrial and arterial switch

Atrial switch

- *Atrial arrhythmias (flutter/fibrillation):* poorly tolerated and prompt restoration to sinus rhythm is essential
- *Baffle narrowing/leaks:* stenosis relieved by transcatheter balloon dilatation/stenting, leaks repaired with stenting or device closure. Surgery may be required if not suitable for catheter intervention
- *Systemic right ventricular failure with tricuspid regurgitation (TR):* valve repair/replacement should be considered for TR with right ventricular ejection fraction ≥45%. Intensive medical therapy (diuretics and heart failure medications), but ultimately may necessitate cardiac transplantation
- *Sinus node dysfunction:* incremental risk with ↑ age. May need permanent pacemaker/implantable cardioverter–defibrillator/cardiac resynchronization therapy defibrillator in atrioventricular block with systemic right ventricular impairment

Arterial switch

- *Supravalvular pulmonary stenosis/branch pulmonary artery stenosis:* consider stenting if >50% diameter narrowing and right ventricular systolic pressure >50mmHg
- *Left ventricular dysfunction/arrhythmia:* secondary to reimplanted coronary arteries
- *Aortopathy and neo-aortic regurgitation:* surgery should be considered if neo-aortic root >55mm
- *Ischaemia:* may need surgery/stenting in coronary artery stenosis

Cyanotic defects: tetralogy of Fallot

Epidemiology

- This is the commonest cyanotic cardiac lesion presenting outside the neonatal period (10% of all CHD).

Pathophysiology

- Comprises a 'tetrad' of non-restrictive VSD, overriding aorta, RVOT obstruction, and RVH.

Associated conditions

- Associated with Noonan, Down, and di George (22q11 deletion) syndromes (see ➔ Genetic syndromes associated with CHD, pp. 380–1).

Clinical features

- Early presentation in infancy is with cyanosis.
- The patient may undergo a palliative BT shunt (see ➔ Surgical operations for CHD, pp. 374–7) prior to surgical repair in early childhood, although this is now uncommon. Instead, an RVOT stent may be placed to alleviate obstruction or early radical repair may be undertaken.
- Signs include diastolic murmur (PR or AR), a harsh ESM (RVOT obstruction), or a pansystolic murmur (VSD).

Complications

- Significant PR (or PS).
- Residual VSD or RVOT obstruction.
- Aortic root dilatation and AR.
- Biventricular systolic dysfunction and consequent HF.
- Arrhythmias (atrial and ventricular), with a risk of SCD.

Investigations

- *ECG:* likely to demonstrate RBBB
- *Echocardiography:* assessment of residual RVOTO, residual PR, residual VSD as well as biventricular function, TR, pulmonary artery pressures, AR and aortic root size.
- *CMR:* may be useful for RV, PV, assessment of PAs, and the conduits and great vessels.
- *CPET:* assessment of arrhythmias and timing of PV intervention.
- *Holter monitoring:* evaluation of arrhythmias.

Management

- *Primary repair:* following palliative procedures in infancy, primary repair takes place between 6 and 18 months. This involves surgical closure of the septal defect and relief of RVOT obstruction. Survival after repair is excellent (35-year survival of 85%).
- *Valve replacement:* indicated in severe PR/PS and/or severe AR (patients likely to require multiple reinterventions during their lifetime due to mean prosthetic valve lifespan).

- *EP studies:* should be considered for those with additional risk factors (QRS duration ≥180ms on ECG, extensive RV scarring on CMR, symptomatic NSVT, LV/RV dysfunction). Ablation may be performed for symptomatic monomorphic sustained VT. Primary prevention ICDs should be considered in those with multiple risk factors for SCD, including those aforementioned, as well as inducible VT.
- *Branch PA stenoses:* should be treated aggressively by catheter intervention.

Cyanotic defects: Fontan circulation

Fontan patients

- A Fontan circulation is the definitive palliation for patients born with 'single ventricle' physiology.
- All systemic venous return is passively directed back to the lungs without the benefit of a subpulmonary ventricle (e.g. mitral/tricuspid/pulmonary/aortic atresia).
- To address the inadequate pulmonary circulation in childhood, staged procedures typically encompass a systemic-to-PA shunt (e.g. BT) followed by Glenn (cavopulmonary) anastomosis before having a Fontan procedure (see ➔ Surgical operations for CHD, pp. 374–7).
- Produces excellent early and mid-term survival, but late failure occurs, even in the most carefully selected candidates.
- The Fontan circulation essentially separates systemic from pulmonary circulation haemodynamically by connecting the systemic venous return directly into the PAs.
- Anterograde pulmonary blood flow therefore depends on the pressure differential between central venous and LA pressure. Optimal CO in Fontan physiology is dependent on the factors illustrated in Fig. 8.6.

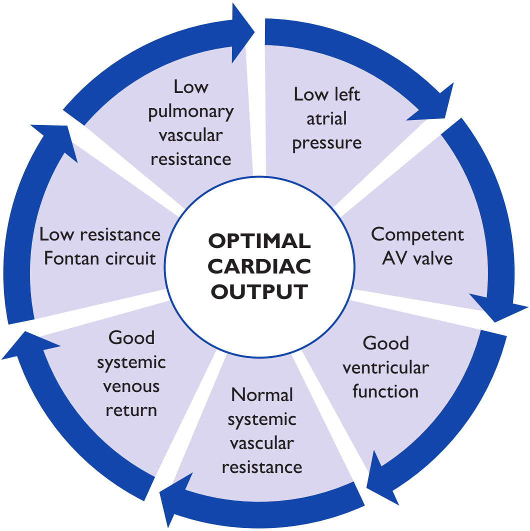
Low pulmonary vascular resistance
Low left atrial pressure
Low resistance Fontan circuit
OPTIMAL CARDIAC OUTPUT
Competent AV valve
Good systemic venous return
Good ventricular function
Normal systemic vascular resistance

Fig. 8.6 Key components for optimizing Fontan physiology.

Complications of Fontan circulation

Arrhythmias

- Atrial tachyarrhythmias are common, particularly in RA–PA Fontans.
- Patients may also exhibit sinus node dysfunction and heart block requiring pacing.
- Depending on the type of Fontan and underlying cardiac anatomy, epicardial pacing may be necessary as transvenous access may not be feasible.

Thrombosis

- RA–PA Fontans are particularly susceptible in view of progressive, massive dilatation of the RA with low-pressure flow.
- Anticoagulation should be considered, especially in the presence of arrhythmia.

Protein-losing enteropathy

- Characterized by hypoalbuminaemia, ascites, and diarrhoea.
- Diagnosis is made from elevated α1-antitrypsin levels in stool.
- Management of protein-losing enteropathy is difficult, with no definitive therapeutic strategy. Treatment options include diuretics, steroids, UFH, octreotide, and a trial of pulmonary vasodilators, such as sildenafil, for afterload reduction.

Ventricular dysfunction

- Both systolic and diastolic dysfunction are recognized, with worse outcomes seen in systemic RVs compared with LVs.
- There is limited evidence for the role of conventional HF treatment with ACEis and β-blockers in Fontan patients.

Fontan-associated liver disease

- ↑ recognized phenomenon in recent clinical practice, with liver screening gradually being incorporated into routine care.
- Hepatic dysfunction is likely multifactorial in aetiology, with a spectrum of disease seen.
- Ranges from deranged LFTs to fibrosis, cirrhosis, and hepatocellular carcinoma.

Atrioventricular valve regurgitation

Formation of collaterals

- Both veno-venous and arteriovenous.
- Reflecting elevated venous pressure.

Plastic bronchitis

- Rare complication in children post-Fontan surgery (even less common in adults), with production of large bronchial casts that obstruct the tracheobronchial tree. This can result in airway obstruction and asphyxiation, which can be life-threatening.

The 'failing Fontan'

- A major challenge with ↑ patient numbers.
- Transplantation or conversion to a more streamlined Fontan modification with concomitant arrhythmia surgery should be considered where appropriate.

Cyanotic defects: Ebstein's anomaly

Epidemiology

- Occurs in 0.005% of live births.

Pathophysiology

- Characterized by abnormal formation and apical displacement of the TV.
- The right heart therefore comprises the RA, the RV, and an atrialized portion of the RV.
- Associated with atrial communication (ASD or PFO), cyanosis occurs via right-to-left shunt at the atrial level.

Clinical features

- There is a wide spectrum of presentation, depending on the severity of TR and associated anomalies.
- *In infancy:* presents with HF and cyanosis, and prognosis is poor. These patients may undergo Fontan palliation.
- *Older child or young adult:* the murmur may be an incidental finding, and mild forms can be asymptomatic or present with fatigue, dyspnoea, chest pain, and cyanosis.
- Clinical findings include cyanosis, hepatomegaly, widely split HS2 (ASD), and pansystolic murmur (TR).

Complications

- Severe TR.
- RV failure.
- Atrial arrhythmias—common and associated with pre-excitation.
- Cerebral abscesses.
- Paradoxical embolism.

Investigations

- *ECG:* RA hypertrophy, prolonged PR/pre-excitation, RBBB.
- *Echocardiography:* anatomy and function of the TV, assessment of the RV and LV.
- *CMR:* may be useful for right heart assessment.

Management

Medical

- Anticoagulation is indicated for those with AF and paradoxical embolism.

Surgical

- Atrial arrhythmias may be amenable to radiofrequency ablation.
- Surgical (Cone) repair (preferable to TV replacement) is warranted in patients with severe TR and symptoms or deterioration of exercise capacity and in those with progressive right heart dilatation.
- Where there is need for TV surgery, ASD/PFO closure should also be considered.

Extracardiac issues in cyanotic CHD

Haematological

Secondary erythrocytosis

- Results from chronic hypoxia; ↑ red cell mass and total blood volume. 'Ideal' Hb for a cyanotic patient depends on their resting SaO_2.
- Hyperviscosity symptoms may develop (e.g. headaches, blurred/double vision, ↓ alertness, fatigue, paraesthesiae, tinnitus, myalgia, TIA/CVA.
- Routine therapeutic phlebotomy not recommended. Those with suspected hyperviscosity should be rehydrated. Venesection only for symptomatic, hydrated, iron-replete patients if haematocrit >65%.
- Symptoms may be relieved by removal of ≤500mL of blood.
- Phlebotomy should be done ≤2/year, as it ↑ the risk of stroke by causing iron deficiency. IV line filters should always be used.

Iron deficiency

- In secondary erythrocytosis, treat aggressively with PO iron supplements (ferrous sulfate 600mg/day). Monitor response to treatment.
- PO iron is often poorly tolerated (abdominal pain, diarrhoea, constipation) and compliance is low. Absorption ↓ in patients with systolic HF, and prolonged courses are needed to correct deficiency.
- This may also be the case in patients with cyanotic heart disease and high venous pressure (liver congestion and high portal pressure).
- IV iron (e.g. Venofer®) is preferred.

Thrombosis and bleeding

- The causes are multifactorial, including a combination of abnormal platelet function, coagulation abnormalities, and polycythaemia.
- Haemoptysis caused by pulmonary haemorrhage is the commonest major bleeding event. Spontaneous bleeding is usually minor.
- Prothrombin time (PT) and activated partial thromboplastin times (APTT) may be ↑, secondary to ↓ factors V, VII, VIII, and X.
- Dehydration or oral contraceptives are risk factors for thrombosis.
- Evidence not supportive of routine anticoagulation in cyanotic CHD.
- Spontaneous bleeding is generally self-limiting. Aspirin and other NSAIDs should be avoided to ↓ spontaneous bruising/bleeding.
- In severe bleeding, general measures are effective, including platelet transfusion, fresh frozen plasma, cryoprecipitate, and vitamin K.

Gallstones

- Common due to ↑ concentration of unconjugated bilirubin from ↑ Hb turnover and hyperuricaemia. Cholecystitis may ensue.

Respiratory

Breathlessness

- May be due to infection, infarction, haemorrhage, pulmonary oedema, or hypoxia (↑ shunt).
- JVP typically ↑ in cyanotic CHD; do not use as only marker of HF. Compare CXR with prior films to assess for pulmonary oedema.
- Patients need ↑ filling pressure to maintain pulmonary blood flow.
- Give high-flow oxygen. Start antibiotics if infection suspected.
- Give PO diuretics if pulmonary oedema or severe right HF.

- Large diuretic/nitrate doses will ↓ BP; may cause acute collapse.
- Monitor haematocrit and renal function for signs of over-diuresis.

Haemoptysis

- See ➜ Emergencies in adults with CHD, pp. 386–7.

Rheumatological

Renal disease and gout

- Hypoxia affects glomerular and tubular function. Results in proteinuria, ↓ urate excretion, and ↓ creatinine clearance.
- Overt renal failure is uncommon.
- Avoid dehydration, diuretics, and radiographic contrast.
- Colchicine/steroids are first line for acute gout; avoid NSAIDs.

Arthralgia

- This is mainly due to hypertrophic osteoarthropathy.
- *Right-to-left shunts:* megakaryocytes bypass the pulmonary circulation, are trapped in systemic vascular beds, and promote new bone formation.

Infection

Skin

- Acne with poor healing is common; may be a nidus for infection.

Sepsis

- ↑ risk infection.
- Dental hygiene important due to the risk of IE.
- Cerebral abscess may occur from disseminated infection/septic emboli. Suspect if fever and headache, especially in cyanotic patients.

Other

Chest pain

- Secondary to PE/infarction (thrombosis), pneumonia, IHD, or musculoskeletal causes.
- Requires careful evaluation with conventional diagnostic modalities.

Stroke

- Can be both thrombotic and haemorrhagic.
- Arterial thrombosis, embolic events (paradoxical emboli in right-to-left shunt), and injudicious phlebotomy lead to spontaneous thrombosis.
- Abnormalities of haemostasis, especially when combined with NSAIDs or formal anticoagulation, can lead to haemorrhagic stroke.
- Injured tissue is a nidus for intracranial infection/abscess formation.

Effort syncope

- Search for arrhythmias, valve disease, or signs of overt HF.

Complications secondary to drugs, investigations, and surgery

- Avoid abrupt changes in BP or systemic resistance.
- Contrast agents may precipitate renal failure or provoke systemic vasodilatation and cause acute decompensation.
- High-flow oxygen is important before and after surgery.
- Extreme caution is required with IV lines to avoid embolic events.

Surgical operations for CHD

- Congenital heart surgery in adolescents/adults should only be undertaken in specialist centres. Patients will fall into three categories:
  - Patients who have not had prior operations (native anatomy)
  - Patients who have undergone previous palliative operations
  - Patients who have undergone previous reparative procedures.
- Redo sternotomy, preservation of myocardial performance, and attention to pulmonary bed vascular abnormalities and aorto-pulmonary collaterals require careful planning and close MDT cooperation.

Blalock–Taussig shunt

(See Fig. 8.7)

- A systemic-to-pulmonary arterial shunt by using a subclavian arterial flap (classical) or Gore-Tex® tube (modified) to the ipsilateral PA.
- ↑ pulmonary blood flow and oxygenation in cyanotic CHD.
- Palliative procedure. Superseded earlier procedures; Waterston shunt (ascending aorta–right PA), Pott's shunt (descending aorta–left PA).

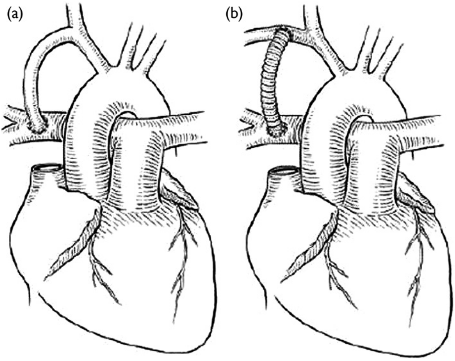

Fig. 8.7 Blalock–Taussig shunt. (a) Original. (b) Modified.

Glenn shunt

(See Fig. 8.8)

- The SVC is anastomosed to the ipsilateral PA to improve oxygenation in infants or young children.
- Used in 'single' ventricle or univentricular circulation.
- *Classical form:* the right PA is detached from the main PA.
- *Bidirectional shunt:* allows blood from the SVC to enter both PAs.

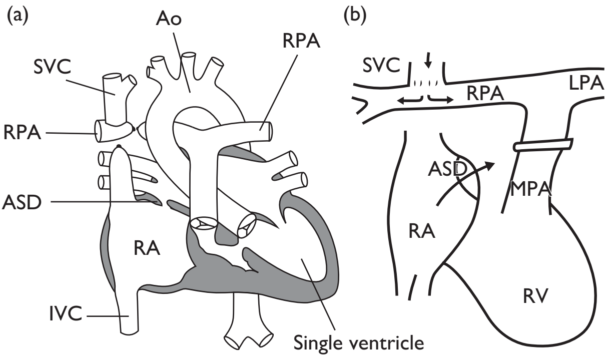

Fig. 8.8 (a) Classic Glenn shunt. (b) Bidirectional Glenn shunt with previous Norwood procedure (surgically enlarged ASD). Ao, aorta; ASD, atrial septal defect; IVC, inferior vena cava; RA, right atrium; RPA, right pulmonary artery; SVC, superior vena cava.

Fontan operation

(See Fig. 8.9)

- Palliative procedure (undertaken since 1968) for effectively univentricular circulations (initially in tricuspid atresia).
- Aims to ↑ oxygen saturations and ↓ ventricular volume overload.
- Staged procedures separate the systemic and pulmonary venous return. Blood from the SVC and IVC directed to the PAs, bypassing the subpulmonary ventricle. Oxygenated blood returns to the systemic ventricle and is then pumped to the aorta.

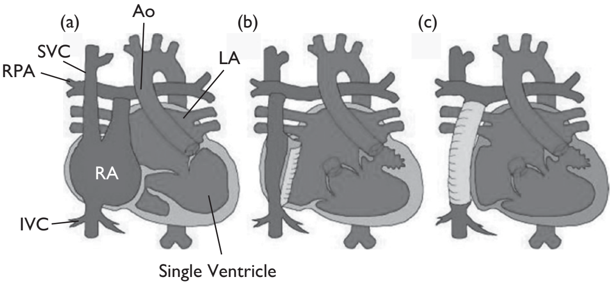

Fig. 8.9 (a) Atriopulmonary Fontan. (b) Lateral tunnel Fontan. (c) Extracardiac Fontan. Ao, aorta; IVC, inferior vena cava; LA, left atrium; RA, right atrium; RPA, right pulmonary artery; SVC, superior vena cava.

Arterial switch

- This has largely superseded the Mustard/Senning procedure for treatment of TGA.
- The aorta and PAs are relocated (LeCompte manoeuvre), with reanastomosis of the coronary arteries to the neo-aorta.

Mustard/Senning operations

(See Fig. 8.10)

- These were lifesaving innovations for treatment of patients with TGA. Involve intra-atrial redirection of oxygenated and deoxygenated blood to the systemic and pulmonary systems, respectively ('atrial switch' procedure).
- Physiological correction is achieved by constructing intra-atrial baffles (surgically created structures to divert blood flow).
- Systemic venous return directed across the left AV valve ('mitral') into the LV and PA. Pulmonary venous return directed across the right AV valve ('tricuspid') into the systemic RV and aorta.
- *Mustard procedure:* synthetic or pericardial patch tissue is utilized to fashion the baffles.
- *Senning procedure:* autologous RA and interatrial septal tissue are used.
- The RV serves as the systemic subaortic ventricle.
- These procedures have been largely abandoned because of late problems with arrhythmias, pathway obstruction, and ventricular failure.

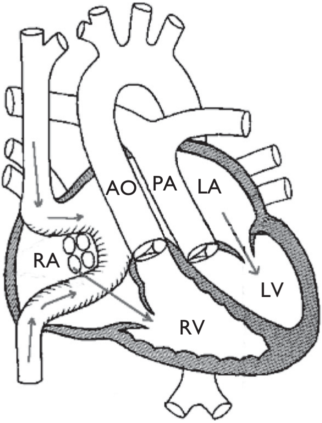

Fig. 8.10 The Mustard/Senning operation.

Rastelli operation

(See Fig. 8.11)

- This is usually undertaken in patients with complex CHD (e.g. TGA with large VSD).
- The VSD is closed by a patch in such a way as to connect the LV to the aorta. A conduit or homograft connects the RV to the PA.

Aortic coarctation repair

- This is surgically relieved by a subclavian flap approach, direct end-to-end anastomosis, prosthetic patch aortoplasty, or insertion of an interposition graft; via left thoracotomy.
- Occasionally, an ascending-to-descending aorta bypass graft is required in adult patients.

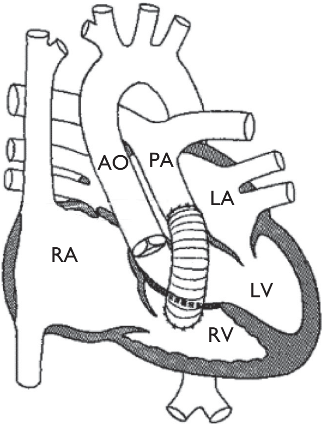

Fig. 8.11 Rastelli operation.

Ross operation

- This is an alternative to aortic valve replacement, which may be attractive to younger patients, especially women.
- The aortic valve is removed, and the coronary arteries detached. The patient's PV is placed in the aortic position, with the coronaries reattached.
- A homograft is placed between the RV and the PA.

Tetralogy of Fallot

(See Fig. 8.12)

- Repair involves closure of the VSD with a pericardial or Gore-Tex® patch and relief of the RVOT obstruction by trans-annular patching, valvectomy, or a homograft/conduit between the RV and the PA.
- Patients are likely to require multiple surgeries during their lifetime, most commonly PV replacement.

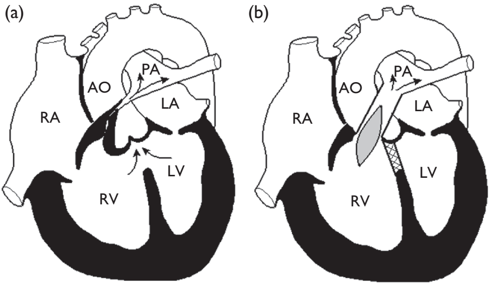

Fig. 8.12 (a) Native tetralogy of Fallot with pulmonary stenosis, overriding aorta, and ventricular septal defect (VSD). (b) Repaired tetralogy of Fallot with the right ventricular outflow tract patch in grey and the VSD patch *in situ*. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

Percutaneous transcatheter interventions for CHD

Balloon atrial septostomy

- This is a lifesaving intervention in neonates with TGA.
- An atrial communication is created in the atrial septum by using a balloon catheter.
- It can be performed at the bedside under echocardiographic control.

Pulmonary valvuloplasty

- This is the procedure of choice for patients of all ages with PS.
- It is less successful if the valve is dysplastic (Noonan syndrome).
- The PV annulus is measured by echocardiography or angiography, and a balloon (100–120% diameter) is used.
- There is a risk of inducing PR.

Aortic valvuloplasty

- This is of limited use in adults.
- If the AV is pliable, but not calcified, balloon dilatation may defer the need for definitive surgery, but usually at the expense of AR.
- The balloon size should not exceed the size of the aorta at the site of the valve attachment. An antegrade approach via a trans-septal puncture is advised, to reduce the incidence of valve damage.

Atrial septal defect

- ASDs may be amenable to transcatheter occlusion using the Amplatzer septal occluder device.

Ventricular septal defect

- Indications for closing defects in adults are limited, and the procedure is most frequently employed in patients with ischaemic VSD.
- Occasionally, ‘small’ defects can produce volume overload of the LV over time and require closure.
- Such defects may be amenable to transcatheter occlusion by using the Amplatzer® perimembranous or muscular occluding devices. This should only be undertaken in specialist centres.
- CHB and device embolization have been described.

Coarctation of the aorta

- Surgical correction in the adult is a major challenge, with its associated risk of paraplegia. The presence of an aortopathy renders the aortic tissue friable.
- Both native CoA and re-coarctation can be successfully treated by transcatheter balloon dilatation and stenting.
- Covered stents may be required for native coarctation to reduce the incidence of dissection and rupture.
- MRI is invaluable for patient selection and stent size selection.
- Stenting of coarctation should only be undertaken in specialist centres where expert surgical help is readily available.
- Balloon dilatation of previous patch aortoplasty carries the highest risk of aortic rupture.

Patent ductus arteriosus

- This may occasionally present in later life.
- If the PDA is small or medium-sized, with LV dilatation and no PHT, most can be successfully occluded with a variety of transcatheter duct occluders or coils.

Pulmonary valve implantation

- Percutaneous techniques have ↓ recovery times, morbidity, and psychological impact on patients, compared with surgical intervention.
- Percutaneous PV implantation has become a viable alternative to surgical valve replacement in congenital patients with PV dysfunction over the past two decades.
- Medtronic Melody® and Edwards Sapien™ valves can be deployed into non-compliant RV–PA conduits of up to 22mm and 29mm in diameter, respectively.
- Novel self-expanding implants for larger native RVOTs are being evaluated to extend the applicability of these percutaneous valves.
- Exclusion criteria for percutaneous PVR include occluded venous anatomy, active infection, unfavourable RVOT morphology (<16mm or >29 mm in diameter), or coronary anatomy at risk during valve implantation.
- Periprocedural complications include valve embolization and conduit rupture, whereas long-term complications include stent fracture, as well as an ↑ incidence of IE.

Genetic syndromes associated with CHD

di George syndrome (22q11 deletion)

- Also known as velocardiofacial syndrome.
- Autosomal dominant inheritance pattern.
- Forty per cent have CHD, in particular conotruncal defects, including ToF, truncus arteriosus, or interrupted aortic arch.
- *Associated non-cardiac features:* palate defects, learning disabilities, psychiatric issues, and thymic hypoplasia with immune deficiency.

Down syndrome (trisomy 21)

- One of the commonest chromosomal abnormalities, with an incidence of 1 per 1000 live births.
- Fifty per cent associated with CHD, most commonly AVSDs, followed by VSD and ASDs.
- Prone to developing pulmonary vascular disease and consequent Eisenmenger syndrome, compared with patients with similar CHD.
- *Associated non-cardiac features:* typical facies, intellectual/learning disability, short stature, hearing loss, and obstructive sleep apnoea.

Marfan's syndrome

- Autosomal dominant disorder of connective tissue, with the majority caused by mutations in the *FBN1* gene encoding fibrillin-1.
- Multiorgan manifestations with CV, skeletal, skin, ocular, and pulmonary abnormalities (see Box 8.6).
- Cardiac sequelae include progressive aortic dilatation leading to aortic dissection or rupture, as well as valvular pathology (AR, MV and/or TV prolapse and regurgitation).

Box 8.6 Summary of revised Ghent diagnostic criteria for Marfan's syndrome

In the absence of family history, these four criteria are diagnostic

- Aortic root dilatation (Z score ≥2) *and* ectopic lentis
- Aortic root dilatation (Z score ≥2) *and* identified *FBN1* mutation
- Aortic root dilatation (Z score ≥2) *and* systemic score ≥7
- Ectopia lentis *and FBN1* mutation with known aortic dilatation

In the presence of family history, these three criteria lead to diagnosis

- Ectopia lentis *and* family history of Marfan's syndrome
- Systemic score ≥7 *and* family history of Marfan's syndrome
- Aortic root dilatation score ≥2 (aged ≥20 years) or ≥3 (aged <20 years) *and* family history of Marfan's syndrome

Noonan syndrome

- Autosomal dominant inheritance, with an incidence of 1 per 1000–2500 live births.
- There is an expanding role for genetic testing in the diagnostic pathway, with 50% having a pathogenic variant of *PTPN11* gene.
- CHD found in 50–80% of individuals, with PS commonest (in 20–50%). Other cardiac defects include ASDs, VSDs, branch PA stenosis, and ToF. HCM affects 20–30% of individuals with Noonan syndrome.
- *Associated non-cardiac features:* characteristic facies (low-set, posteriorly rotated ears, wide-spaced eyes with ptosis and webbed neck), short stature, and developmental delay.

Turner syndrome

- Commonest sex chromosomal abnormality in ♀, with deletion of one X chromosome (45,XO) or mosaicisim. Incidence of 1 per 2000–2500 ♀ live births.
- CHD occurs in 50%, most commonly bicuspid aortic valve, coronary anomalies, CoA, and aortopathy. Serial surveillance should involve treatment and monitoring of systemic hypertension, CAD, and ↑ risk of aortic dissection.
- *Associated non-cardiac features:* typical facies, delayed puberty or primary amenorrhoea, renal anomaly (horseshoe, absent or hypoplastic kidneys), neurocognitive deficits, and lymphoedema.

Williams' syndrome

- Autosomal dominant inheritance, microdeletion disorder with an incidence of 1 per 10,000 live births.
- Cardiac abnormalities include supravalvular AS in 70% of patients, coronary artery stenosis, myxomatous degeneration of the aortic valve and/or MV leaflets, as well as peripheral PA stenosis; 50% develop systemic hypertension.
- *Associated non-cardiac features:* elfin-like features, intellectual disability with sociable 'cocktail party'-type personalities. Other abnormalities include hypercalcaemia, DM, hypotonia, and elevated BMI.

Specific management issues

Arrhythmias

- See ➲ Emergencies in adults with CHD, pp. 386–7.

Pulmonary hypertension

- PHT is defined as ↑ mean PAP of ≥25mmHg by right heart catheterization.
- PHT associated with ACHD (group 1 of PHT classification) comprises a heterogeneous patient population. Reported in 5–10% of patients with ACHD.

Management

- Pulmonary vasodilator therapies (PDE-5 inhibitors, endothelin receptor antagonists, and prostanoids) should be initiated via designated specialist units.
- Eisenmenger syndrome is the most severe form of PAH and should be managed in specialist centres.

Heart failure

- HF patients with ACHD are an expanding population, particularly in univentricular circulation and systemic RV patients.
- The evidence base for HF management in ACHD is limited. This is compounded by the fact that the cardiorespiratory pathophysiology is very different in these patients (e.g. in a Fontan circulation).
- In general, patients with an impaired systemic LV are treated with conventional HF therapy. This also applies to those with symptoms and a failing RV. Diuretics are helpful for symptom control; however, long-term use of ACEis or β-blockers is unknown.
- Additional considerations include CRT, whereas assessment for advanced therapies with inotropes, MCS, and transplantation should be undertaken if appropriate.

Cardiac transplantation

- Historically, rarely undertaken in adults with CHD.
- There are serious considerations for these patients which include: complex anatomy, previous sternotomies, arterial/venous collaterals which ↑ bleeding risk, HLA sensitization from previous blood transfusions, and multiorgan dysfunction in chronic cyanosis.
- There are very limited instances of multiorgan transplants in CHD patients, with heart–lung or in combination with liver/renal transplants.

Infective endocarditis antibiotic prophylaxis

- NICE does not routinely recommend antibiotic prophylaxis for dental procedures.
- In contrast, the ESC guidelines recommend antibiotic prophylaxis for patients at highest risk, which include:
  - Patients with previous IE
  - Patients with prosthetic valve or prosthetic material used for cardiac valve repair

  - Patients with CHD: (1) in cyanotic unrepaired patients or those with residual defects, or palliative shunts or conduits; (2) repaired CHD for 6 months following surgical or percutaneous intervention; (3) presence of residual defect at site of surgically or percutaneously implanted device or prosthetic material.
- Meticulous dental hygiene is essential.

Non-cardiac surgery

- This should be undertaken in specialist centres, with care delivered by an MDT.
- Use local anaesthesia, if possible; otherwise use a cardiac anaesthetist with experience in CHD.
- Air line filters should be employed.
- Special attention should be paid to fluid balance and electrolyte maintenance.

Pregnancy in those with CHD

The majority of women with CHD can tolerate pregnancy. All need specialist counselling and risk assessment, based on modified World Health Organization (mWHO) classification of maternal risk, *before* embarking on pregnancy.

Source: data from ESC Guidelines for management of cardiovascular disease during pregnancy. *Eur Heart J* 2018; **39**(34):3165–3241.

For further details on treatment of CV conditions during pregnancy, see ➔ Chapter 9.

- CHD is a major cause of maternal mortality in developed countries.
- All women of childbearing age should undergo a detailed clinical and haemodynamic assessment, which should include echocardiography, with emphasis on systemic ventricular function, and a formal exercise test. They should be reviewed by a cardiologist with a special interest in maternal cardiology.
- Genetic counselling should be provided, as the average recurrence risk of CHD is 3–5% in the absence of single gene disorders or chromosomal abnormalities. A fetal scan should be offered to those who wish to have one.
- HLA sensitization with pregnancy should be discussed, as it may influence future transplant candidacy.
- Severe cyanosis (saturations <85%) ↑ the risk of miscarriages (<12% chance of live birth) and intrauterine growth retardation.
- All women with complex CHD should be closely monitored in specialist centres where delivery should take place, and MDT input is essential.
- Pregnancy is contraindicated in some CHD patients.

Women with congenital heart disease in whom pregnancy is strongly advised against (mWHO Class IV, maternal cardiac event rate 40–100%)

- PAH:
  - Example: Eisenmenger syndrome (50% maternal and fetal mortality; maternal death may occur up to 2 weeks post-partum)
- Severe systemic ventricular impairment (ejection fraction <30%)
- Severe symptomatic aortic stenosis or mitral stenosis
- Severe aortic dilatation (>45mm in Marfan's syndrome, >50mm in bicuspid aortic valve or tetralogy of Fallot, >20–25mm/m^2 indexed aortic size in Turner syndrome
- Severe (re-)coarctation
- Fontan patient with any complications

Source: data from ESC Guidelines for management of cardiovascular disease during pregnancy. *Eur Heart J* 2018; **39**(34):3165–3241.

Contraception

- Should be tailored to the patient and her cardiac condition.
- Should be reliable and effective, especially in those at high risk of maternal cardiac events.
- For patients at risk of venous or arterial thromboembolism, newer progesterone-only pills (desogestrel) or implants (etonogestrel) are advised.
- Emergency contraception, such as levonorgestrel, can be used when no contraception has been used or when the usual method has failed. It can be taken by all patients.

Emergencies in adults with CHD

- The number of emergency presentations in ACHD patients continues to rise, with the majority of emergency attendances attributable to cardiac complications.
- Adopt a systematic 'ABC' assessment approach, as you would in any medical emergency. Always seek senior in-house input early, and obtain urgent specialist help from the relevant ACHD service.

Tachyarrhythmias

- Arrhythmia is a leading cause of morbidity and mortality, frequently resulting in hospitalization of patients with ACHD.
- It may lead to significant haemodynamic deterioration and can be poorly tolerated, especially in Fontan patients.
- Maintain a high index of suspicion in tachycardic Fontan patients, as slower intra-atrial re-entry tachyarrhythmia circuits in Fontan patients can be mistaken for 'sinus tachycardia'. If available, compare with the patient's baseline ECG as they are often relatively bradycardic.
- Tachyarrhythmias may be due to:
  - Underlying cardiac defect (e.g. atrial isomerism)
  - Intrinsic conduction abnormalities
  - Part of natural history (e.g. haemodynamic changes such as chamber enlargement or scarring)
  - Residual post-operative myocardial injury or scar
  - Abnormal haemodynamics.

Management

- Systematic resuscitation and assessment.
- Treat tachyarrhythmias in accordance with the Resuscitation Council UK algorithms (see ➔ Tachyarrhythmias, pp. 840–1), with prompt DCCV if the patient is haemodynamically unstable.
- Specialist advice is essential—promptly involve ACHD specialists ± electrophysiologists with CHD interest and experience.
- *Fontan circulations:* exercise extreme caution when considering DCCV. The patient's anatomy may not permit transvenous pacing in the event of CHB post-cardioversion, necessitating external pacing and urgent epicardial pacing wire insertion. If not acutely compromised, it should ideally be undertaken in a tertiary ACHD centre with cardiac surgical availability. Discuss early with ACHD specialists.
- Do not send complex congenital patients in tachyarrhythmias home without specialist input, as they can deteriorate rapidly due to limited physiological reserve.

Haemoptysis

- Haemoptysis can cause significant morbidity and mortality, particularly in those with repaired CoA and cyanotic individuals.

Aetiology

- Most episodes are self-limiting and precipitated by infection. Other causes include:
  - Pulmonary arteriovenous malformations or collateral vessels
  - Embolism of *in situ* PA thrombus
  - Aorto-bronchial fistulae in CoA patients after repair, with erosion of aneurysms that have developed at previous surgical suture lines.

- Differentiation from PE may be difficult. Obtain a detailed history of the patient's congenital diagnoses, and past and recent interventions.
- Knowledge of a cyanotic patient's 'usual' SaO_2 and baseline Hb will aid in management. ↑ Hb levels are needed to maintain oxygen-carrying capacity in cyanotic patients, which may require different thresholds for blood transfusion in discussion with ACHD specialists.

Management

- Systematic resuscitation and assessment.
- Give high-flow oxygen.
- Keep 'nil by mouth'. Severe haemoptysis may require intubation.
- Gain large-bore IV access and start fluid resuscitation through an air filter (to prevent paradoxical emboli).
- Check FBC and clotting, and crossmatch blood.
- ↓ threshold for starting antibiotics if clinical suspicion of infection.
- Initiate tranexamic acid if significant pulmonary haemorrhage.
- May need to discontinue aspirin, NSAIDs and PO anticoagulants.
- Perform a CXR followed by urgent CT if evidence of an infiltrate to identify the bleeding source ± interventional radiology involvement for embolization/coiling.

Infective endocarditis

- Patients with ACHD are at variable, but substantially higher, risk of IE, depending on the underlying cardiac diagnosis (see ➔ Infective endocarditis antibiotic prophylaxis, pp. 382–3).

Chest pain: acute coronary syndromes and aortic dissection

- ↑ survival has resulted in older ACHD patients who are at risk of IHD. ACS management should be as per the general population.
- Be aware of the potential of an ACA in certain CHD conditions such as ToF, TGA, and ccTGA (single coronary anatomy). Patients with TGA post-arterial switch are also at risk of ischaemia due to coronary arteries reimplanted in the neo-aorta.
- Chest pain presentations in patients with known aortic coarctation, bicuspid aortic valve, or hereditary aortic syndromes (Marfan, Loeys–Dietz) should prompt urgent assessment for haemodynamic instability and urgent CT angiography to look for aortic dissection (see ➔ Aortic dissection, pp. 856–7).

Emergency presentations following interventions for ACHD

- ACHD patients may present to their local emergency department with complications from recent cardiac interventions. These may include:
  - *Post-surgical issues:* wound infection or breakdown, pleural effusions/haemothorax, atrial arrhythmias, symptomatic heart block, pericardial effusion (commoner following surgical ASD closure)
  - *Post-transcatheter device closure of ASDs, VSDs, and PDAs:* tachyarrhythmia, migraines (ASD patients), heart block (post-perimembranous VSD closure), device embolization (uncommon)
  - *Post-percutaneous intervention:* vascular injury (pseudoaneurysms, arteriovenous fistula), stroke, IE
  - *Pacemaker-related issues* (see ➔ PPM complications of pacing, pp. 680–1).

Chapter 9

Heart disease in pregnancy

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Basic principles

- *Generally rare:* cardiac disease in pregnancy is rare in the UK and Europe, but common in developing countries.
- *Rheumatic heart disease:* has become extremely rare in the UK; however, it is still prevalent within immigrant populations.
- *Congenital heart disease:* women having undergone corrective or palliative surgery in childhood survive into adulthood and are encountered more frequently. These women may have complicated pregnancies.
- *Hypertensive disorders:* hypertension is common and affects 5–10% of pregnancies. This is associated with pre-eclampsia and can have significant effects on both mother and offspring.
- *Prosthetic valves:* women with metal prosthetic valves face difficult decisions regarding anticoagulation in pregnancy.
- *IHD:* accounts for >20% of maternal deaths. A higher prevalence of CVD is seen with ↑ maternal age. As mean maternal age ↑, this is becoming more common.
- *Aortic dissection:* occurs more commonly in pregnancy (including branch dissection).
- *Peripartum cardiomyopathy (PPCM):* pregnancy may cause a specific dilated cardiomyopathy.
- *Maternal mortality:* despite its relative rarity, cardiac disease is the leading cause of maternal death in the UK, being responsible for 2.3 deaths per 100,000 (2013–15 inclusive).[1]
- *Aetiology:* the predominant cardiac causes of maternal death in the UK are PPCM, MI, and dissection of the aorta and its branches.
- *Benign findings:* because of physiological changes in pregnancy, symptoms such as palpitations and signs such as an ejection systolic murmur are very common and generally innocent findings.
- *Care requirements:* care of the pregnant and parturient woman with heart disease requires a multidisciplinary approach and formulation of an agreed and documented management plan encompassing management of both planned and emergency delivery.

Reference

1. Knight M, Nair M, Tuffnell D, Shakespeare J, Kenyon S, Kurinczuk JJ (eds); on behalf of MBRRACE-UK (2017). *Saving Lives, Improving Mothers' Care: lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2013–15*. Oxford: National Perinatal Epidemiology Unit, University of Oxford.

Physiological changes in pregnancy

There are multiple changes to the CV system in pregnancy to meet the metabolic demands of the mother and fetus (see Table 9.1).

Cardiac output

- CO ↑ early in pregnancy.
- This reaches a maximum (40–50% above baseline) by the mid-second trimester; 75% of this ↑ occurs during the first trimester.
- This is achieved by ↑ SV (during the first half of pregnancy) and ↑ HR (from the second trimester onwards).
- There is atrial and ventricular dilatation, with preservation of ventricular function.
- Underlying cardiac disease may lead to suboptimal adaptation.

Systemic resistance

- There is peripheral vasodilatation, and a fall in systemic vascular resistance.

Pulmonary vasculature

- ↓ pulmonary vascular resistance and colloid osmotic pressure.
- The colloid oncotic pressure–PCWP gradient is reduced by ~25%, making pregnant women susceptible to pulmonary oedema.
- Pulmonary oedema will be precipitated if there is either ↑ cardiac preload (such as from infusion of fluids) or ↑ pulmonary capillary permeability (such as in pre-eclampsia), or both.

Venous return

- In late pregnancy, in the supine position, pressure of the gravid uterus on the IVC causes a reduction in venous return to the heart and a consequent fall in SV and CO. Turning from lateral to supine position may result in 25% reduction in CO.
- Pregnant women should be nursed in the left lateral position wherever possible.
- If the mother has to be kept on her back, the pelvis should be rotated, so that the uterus drops forward and CO, as well as uteroplacental blood flow, is optimized.
- Reduced CO is associated with reduction in uterine blood flow and placental perfusion; this can compromise the fetus.

Labour

- Labour is associated with further ↑ in CO (15% in the first stage and 50% in the second stage).
- Uterine contractions lead to autotransfusion of 300–500mL of blood back into the circulation, and the sympathetic response to pain and anxiety further increases HR and BP.
- CO is ↑ further during contractions, but also between contractions.
- Following delivery, there is an immediate ↑ in CO due to relief of IVC obstruction and contraction of the uterus that empties blood into the systemic circulation. ↑ CO by 60–80%, followed by a rapid decline to pre-labour values within about 1h of delivery.

- Those women with CV compromise are most at risk of pulmonary oedema during the second stage of labour and the immediate postpartum period.

Table 9.1 Physiological changes in the cardiovascular system in pregnancy

Measurement	Change	Details
Cardiac output	↑	40%
Stroke volume	⇄	
Heart rate	↑	5–10bpm[1]
Blood pressure	↓	Mild reduction in first and second trimesters
	↔	Third trimester
Central venous pressure	↔	
SVR and PVR	↓	25–30%
Serum colloid osmotic pressure	↓	10–15%

SVR, systemic vascular resistance; PVR, peripheral vascular resistance.

Reference

1. Loerup L, Pullon RM, Birks J, *et al*. Trends of blood pressure and heart rate in normal pregnancies: a systematic review and meta-analysis. *BMC Medicine*. 2019;**17**:167.

Normal findings in pregnancy

On examination

Findings may include:

- Bounding/collapsing pulse
- Ejection systolic murmur (present in over 90% of pregnant women; may be quite loud and audible all over the precordium)
- Third heart sound
- Relative sinus tachycardia
- Ectopics
- Peripheral oedema.

On ECG

The heart rotates to the left and generally results in a 15–20° leftward deviation of the axis. Potential findings are partly related to changes in cardiac position and include:

- Q wave (small) and inverted T wave in lead III
- Inverted T waves in leads V1 and V2, and sometimes in lead V3
- Transient ST-segment changes
- Atrial and ventricular ectopics (common).

ECG changes should be considered in light of the complete clinical picture. Changes that are normal in pregnancy may require consideration of further investigation in selected patients.

Safety of investigations in pregnancy

Safety of ionizing radiation in pregnancy

- Effect of radiation depends on the stage of pregnancy and dose.
- Risks are low in the second trimester and lowest in the third trimester.
- Radiation-induced abnormalities typically occur at doses of 100–200mGy; 1–2 cases of childhood cancer per 3000 children exposed to 10mGy of radiation *in utero* have been reported.[1]
- The amount of radiation received by the fetus during a maternal CXR is negligible, and CXRs should never be withheld if clinically indicated in pregnancy.
- If clinical suspicion suggests the presence of PE, CTPA or V/Q scanning should be undertaken (ESC Class IIa recommendation). Although there are concerns about radiation exposure to breast tissue in pregnancy, new low-radiation dose protocols have mitigated this significantly.

Safety of other investigations

- TTE and TOE are also safe, with the usual precautions to avoid aspiration.
- MRI is safe in pregnancy.
- Routine investigation with EP studies and angiography is normally postponed until after pregnancy but should not be withheld in, for example, ACS.
- If angiography is undertaken, radiation exposure to the fetus should be minimized (see Box 9.1).

Box 9.1 Minimizing radiation during coronary angiography

When coronary angiography is indicated in pregnancy, the following techniques should be used to minimize radiation doses to the fetus.

- Echocardiographic guidance should be used where possible.
- The radiation source should be placed as far as possible away from the patient.
- The receiver should be placed as close as possible to the patient.
- Only low-dose fluoroscopy should be used.
- Anteroposterior projections should be favoured.
- Direct radiation to the abdomen should be avoided.
- The image should be tightly collimated to the region of interest.
- Fluoroscopy time should be minimized.
- The procedure should be undertaken by an experienced cardiologist.

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Reference

1. Boice JD Jr, Miller RW. Childhood and adult cancer after intrauterine exposure to ionizing radiation. *Teratology*. 1999;**59**:227–33.

General considerations in pregnancy

The heart has relatively less reserve than the respiratory system. Women with heart disease may not be able to ↑ their CO adequately to cope with pregnancy and delivery.

Risk of maternal events

The outcome and safety of pregnancy are related to multiple maternal factors. The following are of particular importance:

- Presence and severity of PHT
- Presence of cyanosis
- Haemodynamic significance of the lesion
- Functional class as determined by the level of activity that leads to dyspnoea (NYHA).

Cardiac events, such as stroke, arrhythmia, pulmonary oedema, and death complicating pregnancies, are predicted by the underlying condition (see Table 9.2). Maternal comorbidities, including smoking status and presence of non-cardiac conditions, should be taken into consideration to create an individualized risk assessment.

Fetal outcomes

- Women with CHD are at ↑ risk of having a baby with CHD and should therefore be offered detailed scanning for fatal cardiac anomalies.
- Women with cyanosis (oxygen saturation <80–85%) have an ↑ risk of fetal growth restriction, fetal loss, and thromboembolism secondary to reactive polycythaemia.
- Maternal medication use may also result in fetal outcomes that must be considered.

Pregnancy multidisciplinary team

Women at ↑ risk of complications should be cared for in an expert centre with an MDT. The team should involve:

- Cardiologist—with expertise in cardiology in pregnancy
- Obstetrician—with expertise in women with heart disease
- Anaesthetist
- Additional team members may include: maternal and fetal medicine specialists, geneticists, cardiothoracic surgeons, paediatric cardiologists, etc.

Pregnancy care

- Regular antenatal visits and judicious monitoring to avoid or treat any anaemia, infection, or cardiac decompensation are essential.
- There should be early involvement of obstetric anaesthetists and a carefully documented plan for delivery.
- Women with risk factors for adverse cardiac or obstetric events should be managed and counselled by an MDT, including cardiologists with expertise in pregnancy, obstetricians, fetal medicine specialists, and paediatricians.

Table 9.2 Classification of maternal cardiovascular risk

mWHO	Diagnosis	
I	Arrhythmias	• Isolated atrial/ventricular ectopics
	Valve disease	• Mild pulmonary stenosis/mitral valve prolapse
	Other CHD	• Repaired simple lesions (e.g. ASD, VSD) • Patent ductus arteriosus (small)
	Event rates	3–10%
	Care location	Local hospital, with follow-up once/twice
	Counselling	Yes
II	Arrhythmias	• Most arrhythmias
	Aortic disease	• Turner syndrome without aortic dilatation
	Other CHD	• Unoperated ASD/VSD • Repaired tetralogy of Fallot
	Event rates	8–22%
	Care location	Local hospital, follow-up once per trimester
	Counselling	Yes
II–III	LV function	• LVEF 45–55% • HCM
	Valve disease	• Native/tissue valve disease not WHO I/IV
	Aortic disease	• Marfan syndrome, no aortic dilatation • Aorta <45mm, with bicuspid aortic valve • Repaired coarctation
	Other CHD	• AVSD
	Event rates	13–18%
	Care location	Tertiary centre, follow-up every other month
	Counselling	Yes

(*Continued*)

Table 9.2 *(Contd.)*

mWHO	Diagnosis	
III	Arrhythmias	• Ventricular tachycardia
	Aortic disease	• Moderate aortic dilatation
	LV function	• LVEF 30–45% • Previous PPCM without residual • LVEF
	Valve disease	• Mechanical valves • Moderate MS • Severe asymptomatic AS
	Other CHD	• Systemic RV • Fontan circulation • Unrepaired cyanotic heart disease • Other complex heart disease
	Event rates	21–29%
	Care location	Expert centre, follow-up every 4–8 weeks
	Counselling	Expert counselling required
IV	LV function	• LVEF <30% • Previous PPCM with residual • LVEF
	Valve disease	• Severe MS • Symptomatic AS
	Aortic disease	• Severe coarctation • Severe aortic dilatation • Vascular Ehlers–Danlos
	Other CHD	• Systemic RV with ≥ moderate ↓ function • Fontan with any complication
	Other	• Pulmonary arterial hypertension
	Event rates	36–50%
	Care location	Expert centre, follow-up every 4 weeks
	Counselling	Expert counselling, with discussion of termination

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mWHO, modified World Health Organization; CHD, congenital heart disease; ASD, atrial septal defect; VSD, ventricular septal defect; LV, left ventricular; LVEF, left ventricular ejection fraction; HCM, hypertrophic cardiomyopathy; AVSD, atrioventricular septal defect; PPCM, peripartum cardiomyopathy; MS, mitral stenosis; AS, aortic stenosis; RV, right ventricle.

Preconception counselling and investigation

- All women with known cardiac/aortic disease wishing to get pregnant require preconception counselling.
- Those with a high-risk/significant contraindication for pregnancy should have the risk of pregnancy and the necessity of careful planning discussed at a young age.

Risk estimation

- Estimation of risk is required to provide appropriate counselling.
- The ESC guidelines on CVD in pregnancy suggest that the following investigations are required (at a minimum) to guide risk assessment:
  - ECG
  - Echocardiography
  - Exercise test (see Box 9.2).
- If aortic pathology is present, then CT or MRI is necessary.

Maternal and offspring complications

- Maternal complications depend on the underlying diagnosis (see Table 9.2).
- Offspring complications occur in 18–30% of mothers with heart disease; neonatal mortality in 1–4% of cases.

Topics to be discussed in counselling

- Long-term prognosis.
- Fertility and miscarriage rates.
- Risk of recurrent congenital disease.
- Drug therapy.
- Estimated risks and outcomes.
- Plans for care and delivery during pregnancy.
- Weight loss (if required), smoking cessation, alcohol consumption.

Box 9.2 Exercise testing before and during pregnancy

- An important part of follow-up in women with congenital heart disease or valve disease.
- Should be undertaken in all women who plan pregnancy.
- If already pregnant, submaximal exercise testing (target heart rate 80% of maximum) should be undertaken in asymptomatic women with suspected heart disease.
- There is no evidence that exercise testing ↑ the risk of spontaneous miscarriage.
- Exercise stress echocardiography can also be considered to improve diagnostic accuracy (dobutamine should be avoided).

Source: data from Regitz-Zagrosek V, *et al*. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;**39**:3165–241.

Genetic testing

Risk of inheritance

- In the general population, the risk of a congenital cardiac defect is ~1%.
- The risk ↑ to 3–50% in offspring of parents with congenital cardiac disease.
- Autosomal dominant conditions (e.g. HCM, long QT syndrome) have an inheritance risk of 50%.

Conditions for which genetic testing should be considered

Genetic counselling should be undertaken by an expert. In the first instance, parental testing may be useful to identify a specific genetic variant:

- Known carrier status for pulmonary artery hypertension/pulmonary veno-occlusive disease
- Parents with cardiomyopathies (e.g. HCM or DCM) or channelopathies (e.g. long QT syndrome)
- CHD with associated genetic abnormalities (e.g. bicuspid aortic valve) or when the patient has dysmorphic features, developmental delay, or other non-cardiac abnormalities are present
- In thoracic aortic pathology
- When other family members are affected.

Prenatal genetic testing can be considered when an identified genetic variant has been identified. Counselling should be undertaken in an expert centre with an MDT.

Screening for congenital heart disease

- A 12-week ultrasound scan has a sensitivity of 85% and a specificity of 99% for detecting congenital heart defects. In the UK, detailed assessment of the heart is performed at the 20-week scan.
- In patients with a normal nuchal fold thickness, the incidence of CHD is 1/1000.
- If an abnormality is detected, further detailed screening should be undertaken to determine if non-cardiac abnormalities are present.

Systemic hypertension in pregnancy

Background

- Hypertensive disorders affect 5–10% of pregnancies.
- Most maternal and offspring risks result from the development of severe hypertension or pre-eclampsia.

Maternal risks

- Placental abruption.
- Stroke.
- Organ failure.
- Disseminated intravascular coagulation.

Offspring risk

- Intrauterine growth restriction.
- Prematurity.
- Intrauterine death.

Classification

- *Pre-existing hypertension:* raised BP present prior to pregnancy or developing <20 weeks' gestation. Likely to continue post-partum.
- *Gestational hypertension:* ↑ BP developing >20 weeks' gestation.
- *Pre-eclampsia:* gestational hypertension with proteinuria (>300mg/24h or albumin-creatinine ratio ≥30mg/mmol).
- *Antenatally unclassifiable hypertension:* BP has not been measured until >20 weeks' gestation. Unclear if pre-existing or gestational hypertension. Repeat measurement required ≥6 weeks after delivery.

Diagnosis

- Defined as SBP ≥140mmHg or DBP ≥90mmHg.
- BP should be measured in the sitting position. During labour, it should be measured in the left lateral recumbent position.
- Manual measurement should be undertaken, as automatic devices can under-record the true BP.
- Ambulatory BP monitoring should be used to diagnose hypertension in pregnancy.
- Proteinuria should be assessed regularly. An assessment in early pregnancy should be undertaken to detect underlying renal disease.

Prevention of pre-eclampsia

- Aspirin (100–150mg/day) is recommended in women at high/moderate risk (see Table 9.3) from 12–36 weeks (ESC Class I recommendation).
- Calcium supplementation (>1g/day) may reduce pre-eclampsia risk, particularly in those with low dietary calcium.

Management

Pre-eclampsia

- The only cure is delivery of the placenta.
- If associated with pulmonary oedema, glyceryl trinitrate should be given IV (ESC Class I recommendation).

Table 9.3 Risk factors for pre-eclampsia

High risk	Moderate risk
Any of the following factors	**>1 risk factor present**
• Hypertensive disease in previous pregnancy • Chronic kidney disease • Diabetes mellitus (type 1 or 2) • Pre-existing hypertension • Autoimmune diseases (e.g. systemic lupus erythematosus)	• First pregnancy • Maternal age >40 years • Pregnancy interval >10 years • Body mass index ≥35kg/m^2 at booking • Family history of pre-eclampsia • Multiple pregnancy (e.g. twins)

- Delivery at 37 weeks or expedited if adverse features (e.g. visual disturbance/haemostatic disorders—ESC Class I recommendation).

Severe hypertension

- Defined as SBP of ≥170mmHg or DBP of ≥100mmHg.
- This degree of hypertension should be treated as an emergency and requires hospitalization (ESC Class I recommendation).
- Treatment should be with IV labetalol, PO methyldopa, or PO nifedipine (ESC Class I recommendation).

Mild/moderate hypertension

- Pharmacological treatment should be initiated in those with a BP of ≥150/95mmHg or in those with a BP of >140/90mmHg if they have additional risk factors (see Box 9.3).
- Treatment should be with labetalol, nifedipine, or methyldopa.

Box 9.3 Cases where hypertension treatment should be started at 140/90mmHg

- Gestational hypertension or pre-existing hypertension with additional superimposed gestational hypertension
- Hypertension with subclinical organ damage or symptoms

Post-delivery

- Hypertension is common in the first week after delivery.
- Do not use methyldopa due to higher risk of post-partum depression.
- Breastfeeding does not ↑ BP in the nursing mother. All antihypertensive agents are excreted in breast milk. Most agents are excreted at low doses; propranolol and nifedipine have similar concentrations in breast milk and plasma.

Pulmonary hypertension in pregnancy

Background

- Pulmonary vascular disease is extremely dangerous in pregnancy.
- May be secondary to a reversed large left-to-right shunt such as a VSD (Eisenmenger's syndrome) or to lung or connective tissue disease (e.g. scleroderma), or due to primary PHT.
- PHT is defined as a non-pregnant elevation of mean (not systolic) pulmonary artery pressure of ≥25mmHg at rest or 30mmHg on exercise in the absence of a left-to-right shunt.
- Pulmonary artery systolic pressure is estimated by using Doppler ultrasound to measure the TR jet velocity.

Maternal risk

- Women with known pulmonary vascular disease should be advised to avoid pregnancy and be given appropriate contraceptive advice.
- Maternal mortality is 16–30%.[1]
- If pregnancy occurs, termination should be discussed.
- Most fatalities occur in the early post-partum period. Danger relates to fixed pulmonary vascular resistance and an inability to ↑ pulmonary blood flow with refractory hypoxaemia. Most deaths are attributed to thromboembolism, hypovolaemia, or pre-eclampsia.

Offspring risk

- Mortality ranges from 0% to 30%. Rates are ↑ by preterm delivery, reduced maternal CO, and hypoxaemia.

Management

- Investigations should follow the standard pathway for PHT. Right heart catheterization may be needed due to diagnostic uncertainty.
- In the event of unplanned pregnancy, therapeutic termination should be offered. Elective termination carries a 7% risk of mortality, hence the importance of avoiding pregnancy if possible.
- Assessment of RV function and oxygen saturations are required at each clinic visit.
- Anticoagulation should be considered, as patients are at ↑ risk of thromboembolic disease.
- Endothelin receptor antagonists can cause embryopathy and should generally be stopped if pregnancy is continued. However, if this would greatly ↑ maternal risk, continuation can be considered.
- There are inadequate human data regarding the safety of phosphodiesterase type V inhibitors (e.g. sildenafil) in pregnancy; however, they are commonly prescribed in some units.
- Multidisciplinary care and a detailed delivery plan are required.
- There is no evidence that the mode of delivery (abdominal/vaginal) or type of anaesthesia (regional/general) improves outcome in PHT.
- In severe PHT after delivery, strongly consider monitoring (HDU) to allow for careful fluid balance for several days.

Reference

1. Sliwa K, van Hagen IM, Budts W, *et al*. Pulmonary hypertension and pregnancy outcomes: Data from the Registry of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. *Eur J Heart Fail*. 2016;**18**:1119–28.

Aortic disease and pregnancy

General maternal risk

- Risk of dissection ↑ due to haemodynamic and hormonal changes.
- Aortic dissection most likely in the third trimester or early post-partum.
- Women with genetic syndrome or familial pathology should have pre-pregnancy counselling, including imaging of the entire aorta.
- Aortic dissection should be considered in all pregnant women presenting with chest pain.

Marfan syndrome and pregnancy

- Affects 1 in 5000 individuals.
- Overall risk of aortic dissection during pregnancy in Marfan syndrome is ~3%. The primary risk factor is aortic root size.
- Pregnancy should be avoided when the aortic root is >45mm in diameter until after root repair/replacement. If 40–45mm, then pregnancy should be avoided if high growth rate or family history of dissection.
- Dissection of other vessels is also a risk.

Bicuspid aortic valve

- Affects 1–2% of the population.
- Dissection can occur even with normal valve function. However, the risk is generally small.
- Pregnancy should be avoided when the aortic diameter is >50mm.

Ehlers–Danlos syndrome

- Vascular complications occur primarily with EDS type IV.
- Significant maternal mortality due to uterine rupture ± arterial or venous dissection.
- Women with EDS should be strongly advised to avoid pregnancy, but a shared decision-making process should be used.

Turner syndrome

- ↑ risk of CHD, including aortic dilatation.
- Dissection is rare. More common if the patient has aortic dilatation, coarctation of the aorta, and bicuspid aortic valve.
- Natural pregnancy occurs in only 2–5% of those with Turner syndrome (mainly in those with mosaicism). However, pregnancy can occur through fertility treatments. Pregnancy should be avoided if the aorta is >25mm/m^2.

Management

- *Monitoring*: regular echocardiography during pregnancy and up to 6 months post-partum. Monthly TTE recommended in those with a severely dilated aorta; 3-monthly TTE may be sufficient if only mild dilatation in low-risk women.
- *Hypertension control:* strict control required with β-blockers to reduce the risk of progressive dilatation. Fetal monitoring is required for patients on β-blockers.
- *EDS type IV:* celiprolol should be prescribed, even if not hypertensive.

- *Intervention timing:* if progressive dilatation prior to viability, surgery with the fetus *in utero* should be considered. If the fetus is viable, then a caesarean section followed by aortic surgery should be undertaken.
- *Dissection management:* should be managed as in non-pregnant patients. Type A dissection requires urgent surgery, and a viable fetus should be delivered emergently by caesarean section. Type B dissection requires aggressive BP control with non-selective β-blockade.

Delivery

- *β-blockers:* should be continued through the peripartum period.
- *Aorta 40–45mm:* vaginal delivery with short second stage. Epidural can be considered to reduce BP spikes.
- *Aorta >45mm:* caesarean section should be considered.
- *EDS:* in those with EDS type IV, caesarean section is recommended.

Mitral stenosis and pregnancy

- Primarily caused by RHD; is uncommon in Europe and North America.
- Important in pregnancy because women may deteriorate secondary to tachycardia, arrhythmias, or ↑ CO during pregnancy even if initially asymptomatic.

Maternal risk

- HF develops in one-third of patients with severe MS (valve area ≤1cm^2).
- Mortality is 0–3% in Europe.
- Sustained AF is uncommon (<10% of cases) but can precipitate HF and thromboembolism.
- Complications associated with older age, NYHA class ≥II, systolic pulmonary artery pressure >30mmHg, and severe stenosis.

Offspring risk

- Prematurity rates reported at 20–30%.
- Risk of intrauterine growth restriction in 5–20% of cases.
- Fetal death in 1–5% of cases.
- ↑ risk in women who have NYHA class III/IV symptoms in pregnancy.

Management

- *Counselling:* women with severe MS should be advised to delay pregnancy until after valvotomy or, if the valve is not amenable to valvotomy, until after MV replacement.
- *β-blockers:* ↓ HR, ↑ diastolic filling time, and ↓ risk of pulmonary oedema. Should be prescribed to those with symptoms or if systolic pulmonary artery pressure ≥50 mmHg.
- *Diuretics:* should be continued if already required. Should be started if the patient becomes symptomatic. High doses should be avoided.
- *Anticoagulation*: should be used/considered in certain situations (see Box 9.4). Use LMWH or VKA according to context and stage of pregnancy.
- *Intervention:* balloon mitral valvotomy may be safely and successfully used in pregnancy if the valve is suitable. Should be undertaken after 20 weeks' gestation. Medical therapy should be attempted first (see Box 9.5). Percutaneous balloon valvotomy carries a risk of major complications of about 1%, whereas for surgical valvotomy, the figures are: closed valvotomy—fetal mortality 5–15%, maternal mortality 3%; open valvotomy—fetal mortality 15–33%, maternal mortality 5%.
- *Follow-up:* monthly clinical and echocardiographic assessment is required in severe MS. In those with mild disease, assessment once per trimester and prior to delivery is sufficient.
- *Labour and delivery:* women with MS should avoid the supine and lithotomy positions as much as possible for labour and delivery. Fluid overload must be avoided, and even in the presence of oliguria, without significant blood loss, the temptation to give IV fluids must be resisted. Vaginal delivery is recommended for mild MS and patients with significant MS and NYHA class I/II symptoms without PHT. Those with significant symptoms or with PHT are generally considered for caesarean section.

Box 9.4 Indications for anticoagulation in mitral stenosis

Should be used

- Atrial fibrillation (paroxysmal or persistent)
- Left atrial thrombosis
- Prior embolism

Should be considered

- Severe mitral stenosis with spontaneous echocardiographic contrast
- Large left atrium (≥60mL/m^2)
- Congestive heart failure

Source: data from Regitz-Zagrosek V, *et al*. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;**39**:3165–241.

Box 9.5 Indications for intervention in mitral stenosis

- NYHA class III/IV symptoms
- Systolic pulmonary artery pressure ≥50mmHg

Source: data from Regitz-Zagrosek V, *et al*. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;**39**:3165–241.

Other valve lesions

Mitral regurgitation

- Most commonly due to MV prolapse, RHD, or degeneration.

Maternal risk

- Well tolerated as systemic vascular resistance is low in pregnancy. LV function is important in assessing risk (normal function carries a good prognosis).
- Fluid overload occurs in 20–25% of women with severe rheumatic MR.

Offspring risk

- Intrauterine growth restriction in 5–10% of cases. Other complications <5%.

Management

- Pre-pregnancy valve repair should be considered (see ➔ Mitral regurgitation: management, pp. 204–5).
- If acute severe MR develops that is refractory to HF therapy, surgery may be required. Ideally delivery should be undertaken prior to cardiac surgery.
- *Follow-up*: patients with mild or moderate disease should have echocardiography and clinical assessment each trimester. More severe disease warrants closer follow-up.
- *Delivery*: vaginal delivery with epidural and shortened second stage is recommended.

Aortic stenosis

- Most commonly due to bicuspid aortic valve or RHD.

Maternal risk

- Depends on severity of stenosis.
- Poor outcomes are uncommon in those with moderate AS and those asymptomatic before pregnancy.
- Severe AS is generally well tolerated if exercise tolerance is normal prior to pregnancy.

Offspring risk

- If the mother has ≥ moderate AS, 20–25% of offspring have preterm birth, intrauterine growth restriction, or low birthweight.
- Miscarriage/fetal mortality <5%.

Management

- If severe and symptomatic, advise deferring pregnancy until surgically corrected. If already pregnant and symptomatic early on, consider termination.
- If fluid overload develops, diuretics should be given.
- Percutaneous valvuloplasty can be considered in patients who are severely symptomatic but is associated with significant risk. There are limited data regarding TAVI during pregnancy.
- If percutaneous intervention is not possible and symptoms are life-threatening, surgical replacement should be considered following early delivery.

- *Follow-up:* in severe AS, monthly echocardiographic and clinical assessment is required.
- *Delivery:* in severe symptomatic AS, delivery should be by caesarean section.

Aortic regurgitation

- Most commonly due to valve degeneration or RHD.

Maternal risk

- Usually well tolerated as reduced systemic vascular resistance in pregnancy reduces the regurgitant volume.

Offspring risk

- No ↑ risk of obstetric complications has been reported.

Management

- If fluid overload develops, vasodilators/diuretics are usually sufficient treatment (stop ACEis and replace with nifedipine, hydralazine, etc.).
- *Follow-up:* patients with mild or moderate disease should have echocardiography and clinical assessment each trimester. More severe disease warrants closer follow-up.
- *Delivery:* vaginal delivery with epidural and shortened second stage is recommended.

Prosthetic heart valves in pregnancy

Choice of valve at time of replacement

- In women who wish to become pregnant in the future, the choice of valve prosthesis needs to be carefully considered.
- Mechanical valves offer excellent performance and durability. However, anticoagulation with warfarin is required, which ↑ maternal and fetal mortality/morbidity.
- Bioprosthetic valves have an ↑ risk of deterioration and ↑ the chance of going through pregnancy with a poorly performing valve.
- It is recommended that an obstetric/cardiology/maternal medicine MDT is involved in these decisions in women who may wish to become pregnant in the future.

Bioprosthetic valves and pregnancy

- The risk of complications is generally low if there is minimal prosthesis dysfunction and normal ventricular function.
- Pre-pregnancy assessment, medical treatment, and indications for intervention are similar to native valve disease.

Mechanical prostheses and pregnancy

- Such women require lifelong anticoagulation, and this must be continued in pregnancy due to ↑ risk of thrombosis (see Box 9.6).
- Warfarin is associated with warfarin embryopathy if given between 6 and 12 weeks' gestation, and ↑ the risk of miscarriage, stillbirth, and fetal intracerebral haemorrhage.
- There is some evidence that the adverse effects of warfarin are related to the dose required to maintain the INR >2, with doses in excess of 5mg being associated with higher risks of teratogenesis, miscarriage, and stillbirth.
- UFH and LMWH, even in full anticoagulant doses, are associated with ↑ risk of valve thrombosis and embolic events.

Anticoagulation management

- Preconception counselling should be undertaken, and warfarin should be continued until pregnant.
- All women should be switched to LMWH/UFH at 36 weeks due to delivery risk on warfarin (ESC Class I recommendation) (see Box 9.7).
- If the dose of warfarin is <5mg/day, continuation of warfarin to 36 weeks should be considered (ESC Class IIa recommendation).
- If the warfarin dose is ≥5mg/day, there are three basic options:
  - Continue warfarin until 36 weeks (ESC Class IIb recommendation). This is safest for the mother, but risk of embryopathy.
  - Replace warfarin with high-dose UFH or LMWH from 6 to 12 weeks' gestation to avoid warfarin embryopathy before reverting to warfarin until 36 weeks (ESC Class IIa recommendation).
  - Use high-dose UFH or LMWH throughout pregnancy (ESC Class IIb recommendation).

Management of delivery

- For delivery itself, heparin therapy is interrupted. LMWH should be stopped 24h before delivery and can be restarted 24–48h after delivery if no bleeding. UFH should be stopped 4–6h before delivery and restarted 4–6h after delivery if no bleeding.

- Warfarin can be restarted 3–5 days post-partum if not bleeding (ESC guidelines). NICE recommends considering delaying until 7 days.
- In the event of bleeding, or the need for urgent delivery in a fully anticoagulated patient, warfarin may be reversed with fresh frozen plasma (FFP) and vitamin K, and heparin with protamine sulfate.
- Vitamin K should be avoided, if possible, as it renders the woman extremely difficult to anticoagulate with warfarin after delivery.

Box 9.6 Appropriate anticoagulation in pregnancy

The option chosen will depend on several factors:

- *Type of valve:* the risk of thrombosis is less with the newer bileaflet valves (e.g. CarboMedics) than with the first-generation ball-and-cage (e.g. Starr–Edwards) or second-generation single-tilting disc (e.g. Bjork–Shiley) valves
- *Valve position:* valves in the aortic, rather than mitral, position are associated with a lower risk of thrombosis
- Number of mechanical valves
- Dose of warfarin required to maintain INR
- Previous history of embolic events

Box 9.7 Anticoagulants in pregnancy

- *LMWH:* effective anticoagulant. Does not cross the placenta. Good bioavailability following subcutaneous administration. Easy weight-based dosing schedule. Thrombocytopenia and osteoporosis are extremely rare. *Side effects:* maternal haemorrhage, wound haematoma, local allergic reaction at injection site.
- *UFH:* rarely used as LMWHs have become available. Use in pregnancy is mainly confined to acute management of massive pulmonary emboli and in the peripartum period, it is used for rapid control (and reversal) of anticoagulation in case emergency delivery is required. *Side effects:* maternal haemorrhage, thrombocytopenia (monitor full blood count), osteoporosis, alopecia.
- *Warfarin:* effective oral anticoagulant. Crosses the placenta. ↑ risk of miscarriage and stillbirth. Studies show it to be more effective than UFH at preventing valve thrombosis in pregnancy. *Side effects:* fetal and maternal haemorrhage, teratogenic in first trimester—therefore avoid during this period if at all possible (use LMWH).
- *Aspirin:* additional low-dose aspirin has no benefit in preventing valve thrombosis. Associated with significant ↑ in maternal bleeding

Coronary artery disease

- Pregnancy is associated with significantly ↑ risk of acute MI.
- Although uncommon, CAD accounts for >20% of maternal deaths.

Aetiology

- Risk factors for CAD are similar to those of the general population.
- Additional pregnancy-related risk factors include:
  - Pre-eclampsia
  - Thrombophilia
  - Transfusion
  - Post-partum infection
  - Multiparity
  - Post-partum haemorrhage
  - Cocaine use.
- The majority of acute MI in pregnancy is non-atherosclerotic: spontaneous coronary artery dissection, normal coronary arteries, and coronary thrombosis.

Clinical findings

- Infarction most commonly occurs in the third trimester or post-partum.
- Presentation is generally similar to a non-pregnant population.
- *ECG:* inverted T waves are common in pregnancy in the absence of ischaemia. Anaesthetic induction for caesarean section can be associated with ST-segment depression.
- *Troponin:* is not ↑ by normal pregnancy, normal delivery, or caesarean section. Can be ↑ in pre-eclampsia. Any rise should be taken seriously and acute MI should be considered.
- The maternal death rate is about 10%.

Management of acute myocardial infarction

- Management of ACS is as for the non-pregnant woman.
- *Angiography:* should not be withheld if clinically indicated.
- *Percutaneous coronary angioplasty:* has been successfully performed in pregnancy. Previously, bare metal stents were preferred; however, recent guidelines have suggested that drug-eluting stents should be used, as the duration of DAPT required is significantly less in second/third-generation drug-eluting stents.
- *Tissue plasminogen activator:* does not cross the placenta. However, it can induce bleeding.
- *β-blockers:* appropriate to use in pregnancy but can be associated with growth restriction.
- *Aspirin:* safe in pregnancy.
- *Other antiplatelet agents:* clopidogrel felt to be safe, although it should be discontinued prior to delivery because of ↑ bleeding risk. Glycoprotein IIb/IIIa inhibitors, ticagrelor, and prasugrel should be avoided due to limited data.
- *DAPT duration:* shorter durations should be considered unless high thrombotic burden.

- *Statins:* limited data. Small cohorts have suggested no ↑ in fetal malformation. Should not be prescribed during pregnancy or breastfeeding.

Pre-existing coronary artery disease

- Reported maternal mortality of up to 25%.
- Highest risk in those with atherosclerotic CAD.
- Unclear how long pregnancy should be delayed after MI. However, ESC suggests a minimum of 12 months.
- If previous pregnancy-induced spontaneous coronary artery dissection, avoidance of further pregnancy is advised.

Labour/delivery

- Acute MI treatment should not be delayed for delivery.
- Delivery should ideally be postponed, where possible, for ≥2 weeks after acute MI.
- Vaginal delivery is preferable.

Breastfeeding

- Not recommended if the mother is taking additional antiplatelet agents to low-dose aspirin.

Hypertrophic cardiomyopathy

- The danger of HCM in pregnancy relates to LVOTO that may be precipitated by hypotension or hypovolaemia.
- Provided these are avoided, pregnancy is usually well tolerated.
- Incidence in pregnancy <1 in 1000.

Maternal risk

- Normally tolerated well.
- Mortality estimated at 0.5%.
- Complications or worsening symptoms in ~30%.

Offspring risk

- ↑ risk of premature birth ~25%.

Prognostic factors

- Symptomatic pre-pregnancy.
- Diastolic dysfunction.
- Severe LVOTO.
- Medication required for HCM prior to pregnancy.
- ZAHARA score ≥1 (see Box 9.8).

Management

- Regular monitoring throughout pregnancy by the pregnancy heart team:
  - *Modified WHO (mWHO) class II:* assessed each trimester.
  - *mWHO class III:* assessed monthly.
- *β-blockers:* should be continued in pregnancy or initiated for symptomatic women (AF rate control or to suppress ventricular arrhythmias).
- *Cardioversion:* consider if persistent AF not well tolerated.
- *Anticoagulation:* required if develops AF.

Box 9.8 ZAHARA score in pregnancy

Characteristic	**Points**
History of arrhythmias	1.50
Cardiac medication before pregnancy	1.50
NYHA class prior to pregnancy ≥II	0.75
LHO (PG >50mmHg or AVA <1.0cm^2)	2.50
Syst AV valve regurgitation (moderate/severe)	0.75
Pulm AV valve regurgitation (moderate/severe)	0.75
Mechanical valve prosthesis	4.25
Cyanotic heart disease (corrected/uncorrected)	1.00
Total number of points 0–13	

NYHA, New York Heart Association; LHO, left heart obstruction; PG, peak gradient; AVA, aortic valve area; AV, atrioventricular; Syst, systemic; Pulm, pulmonary.

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Delivery

- *Low-risk cases:* can be managed with spontaneous vaginal delivery.
- *Caesarean section:* should be considered if severe LVOTO, preterm labour on anticoagulation, or severe HF.
- *Epidural anaesthesia/analgesia:* carries the risk of vasodilatation and hypotension, with consequent ↑ LVOTO. Any hypovolaemia will have the same effect and should be rapidly and adequately corrected (see ➔ Left ventricular outflow tract obstruction, pp. 246–7).

Peripartum cardiomyopathy

- Pregnancy-specific condition.
- Defined as the development of cardiac failure towards the end of pregnancy or in the months after giving birth, in the absence of an identifiable cause or recognizable heart disease prior to the last month of pregnancy, and LV systolic dysfunction.
- The diagnosis should be suspected in the post-partum patient with breathlessness, tachycardia, or signs of HF.
- It is confirmed with echocardiography.

Risk factors

- Multiparity.
- African/Afro-Caribbean ethnicity.
- Smoking.
- Diabetes mellitus.
- Pre-eclampsia.
- Malnutrition.
- Age—either older or teenage.

Clinical features

- Normally features are typical for CCF.
- Other presentations include ventricular arrhythmias and cardiac arrest.

Echocardiographic criteria for peripartum cardiomyopathy

- LVEF <45%.
- Fractional shortening <30%.
- LV end-diastolic diameter (LVEDD) >2.7cm/m^2.
- Often, echocardiography shows the heart is enlarged, with global dilatation of all four chambers and markedly reduced LV function.

Prognosis

- Mortality ranges from 2% to 12% at 6 months.
- ~50% of women make a full recovery.
- Prognostic factors are outlined in Box 9.9.
- Subsequent pregnancies should be counselled against if LVEF has not recovered.

Small chance of recurrence which should be discussed prior to further pregnancies. Should consider stress echocardiography to assess contractile reserve to further risk-stratify prior to subsequent pregnancy.

Box 9.9 Poor prognostic features in peripartum cardiomyopathy

- Initial left ventricular ejection fraction <30%
- Left ventricular end-diastolic diameter ≥6.0cm
- Right ventricular involvement
- Incomplete recovery of left ventricular function on medical management

Heart failure–pregnancy management

- *PO HF therapy:* β-blockers, diuretics, hydralazine, and nitrates should be used as indicated for HF. ACEis can be given if post-partum (enalapril or captopril preferred).
- *Bromocriptine:* should be added to standard HF therapy in PPCM. In uncomplicated cases, 2.5mg od for 1 week. When LVEF <25% or cardiogenic shock, 2.5mg bd for 2 weeks followed by 2.5mg od for 6 weeks should be considered. Treatment must be accompanied by (at least) prophylactic anticoagulation.
- *Anticoagulation:* should follow standard indications for patients with DCM or PPCM. In PPCM with very low LVEF, prophylactic anticoagulation should be considered.
- *Device therapy:* ICD implantation in the acute setting is not recommended as high chance of recovery. A wearable defibrillator may be considered in those with LVEF <35% for 3–6 months. If LV dysfunction severe after 6–12 months, then ICD/CRT-D should be considered as per usual guidelines (see ➲ Indications for implantable cardioverter-defibrillators, p. 685).
- *Transplantation:* should be considered where mechanical circulatory support not possible/desired. Also consider in patients without recovery at 6–12 months. Box 9.10 discusses pregnancy after transplantation.

Delivery

Haemodynamic instability due to advanced heart failure

- Urgent delivery should be considered (irrespective of gestation).
- Caesarean section recommended.
- Epidural/neuraxial anaesthesia recommended to prevent acute pressure/volume changes.

Stable heart failure

- Vaginal delivery is recommended.

Breastfeeding

- Associated with ↑ metabolic demand. Recommended that discouraging breastfeeding is considered when reduced LVEF and NYHA class III/IV (ESC Class IIb recommendation).

Box 9.10 Pregnancy after transplantation

- Very limited data available
- Requires extensive preconception counselling regarding risk of graft rejection, dysfunction, and infection. Should discuss potential teratogenic effects of immunosuppressive drugs.
- Pregnancy may raise rejection rates, especially if the father has the same human leucocyte antigen as the donor.
- Should be avoided for a minimum of 1 year after transplantation and avoided in those at high risk of rejection (e.g. after peripartum cardiomyopathy).
- Breastfeeding contraindicated as immunosuppressive agents excreted in breast milk.

Arrhythmias in pregnancy

(See Table 9.4)

Table 9.4 Arrhythmic risk management at delivery

Low risk	*Diagnoses*	• AF • LQTS (low-risk) • Wolff–Parkinson–White syndrome
	Delivery recommendations	• 1Consultation with a cardiologist• Delivery as advised by obstetric team
Medium risk	*Diagnoses*	• Brugada syndrome • CPVT • LQTS (moderate risk), patients with ICD • SVT (unstable) • VT, previously stable (including structural heart disease)
	Delivery recommendations	• Consult MDT at specialist centre ± cardiac monitor • Delivery as advised by obstetric team • Cardiac monitor • IV line in place • Preparation of IV adenosine ± β-blocker • External defibrillator available
High risk	*Diagnoses*	• CPVT (high risk) • LQTS (high risk) • Short QT syndrome • VT, if previously unstable • VT in congenital heart disease
	Delivery recommendations	• Consult MDT at specialist centre and cardiac monitor • Caesarean delivery recommended, with delivery in thoracic operating theatre • IV line and arterial line inserted • Prepare IV β-blocker ± antiarrhythmic drugs • External defibrillator available • Potential transfer to cardiac ICU post-partum

AF, atrial fibrillation; LQTS, long QT syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ICD, implantable cardioverter–defibrillator; SVT, supraventricular tachycardia; VT, ventricular tachycardia; MDT, multidisciplinary team.

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- Arrhythmias are more common in pregnancy than in age-matched controls.
- The most common arrhythmias are premature beats (atrial and ventricular) followed by AF and paroxysmal SVT.
- VT and VF are very rare in pregnancy.
- Sinus tachycardia is not uncommon in pregnancy. However, possible causes (haemorrhage, infection, thyrotoxicosis, heart failure, or PE) should be considered.

Clinical features

- Many pregnant women are symptomatic from forceful heartbeats that occur following a compensatory pause after a premature ventricular contraction.
- Most women with symptomatic episodes of dizziness, syncope, and palpitations do not have arrhythmias.

Maternal risk

- AF associated with significant relative ↑ in mortality risk (however, low baseline absolute risk).
- Those with congenital LQTS are at ↑ post-partum risk.
- Arrhythmia is the most common CV event during pregnancy in women with CHD.

Offspring risk

- Paroxysmal SVT associated with ↑ risk of low birthweight, preterm labour, and fetal abnormalities.

Management

- *Amiodarone*: should be avoided in pregnancy due to risk of effects on fetal thyroid function.

Supraventricular tachycardia

- *Pre-pregnancy:* patients with established symptomatic SVT should be considered for ablation prior to pregnancy.
- *Acute management:* IV adenosine should be used to terminate SVT in pregnancy—does not cross the placenta.
- *Secondary prevention:* β1-selective β-blockers or verapamil are first line for patients who do not have Wolff–Parkinson–White (WPW) syndrome.
- *WPW syndrome:* flecainide or propafenone recommended as first line for prevention of SVT.

Atrial fibrillation

- *Acute management:* electrical cardioversion if haemodynamic compromise. Anticoagulation should occur before cardioversion.
- *Anticoagulation:* risk stratification is as for non-pregnant patients. DOACs are contraindicated in pregnancy.
- *Chronic management:* rhythm control is the preferred treatment strategy. β-blockers are the first-line option.

Ventricular tachycardia

- *Pre-pregnancy:* patients with established VT should be considered for ablation prior to pregnancy. ICD recommended prior to pregnancy if clinically indicated.
- *Investigation:* new VT during pregnancy should be investigated for underlying structural causes. If occurring in the last 6 weeks of pregnancy, should rule out PPCM.
- *Acute treatment*: electrical cardioversion is recommended for both stable and unstable VT.
- *Secondary prevention:* β-blockers if LQTS or CPVT—should be continued in the post-partum period; verapamil if idiopathic VT; ICD implantation if required during pregnancy should have echocardiographic guidance. Catheter ablation can be considered in sustained drug-refractory VT (ESC Class IIb recommendation). However, it should be postponed until the second trimester, if possible.

Cardiac arrest in pregnancy

This should be managed according to the same protocols used in the non-pregnant woman,[1] with the following additions:

- *Manual left uterine displacement*: pregnant women (especially those in advanced pregnancy) develop aortocaval compression if lying supine. In non-arrest situations, tilting into the left lateral position can relieve this compression. However, this reduces the force of chest compressions. Lateral displacement of the gravid uterus is essential to relieve aortocaval compression; however, this should not be at the expense of good-quality chest compressions. Manual left uterine displacement should be considered.
- *Obstetric team input:* the most senior member of the obstetric team should be summoned. This is to ensure that obstetric causes of the collapse are considered (e.g. amniotic fluid embolism, massive post-partum haemorrhage) and appropriately treated.
- *Perimortem caesarean section:* delivery of the fetus is often the best way to improve maternal circulation. Caesarean section should begin within 4min of resuscitative efforts, with the aim of delivery within 5min.

Reference

1. Jeejeebhoy FM, Zelop CM, Lipman S, *et al*. Cardiac arrest in pregnancy. A scientific statement from the American Heart Association. *Circulation*. 2015;**132**(18):1742–73.

Infective endocarditis

- IE is very rare in pregnancy and is usually due to pre-existing cardiac conditions or IV drug use.

Maternal and offspring risk

- Maternal and fetal mortality is ~30%.

Prophylaxis

- Current UK recommendations from NICE 2008 are that antibiotic prophylaxis against IE is not required for childbirth. The ESC offers the same advice.
- Prophylaxis during pregnancy is the same as prior to pregnancy (see ➔ Endocarditis prophylaxis—dental, p. 336).

Diagnosis

- IE diagnosis uses the same criteria as in non-pregnant patients.
- Acute valvular regurgitation is poorly tolerated in pregnancy. Embolic events are common in pregnancy.

Treatment

- Treatment should be the same as for non-pregnant patients.
- Tetracyclines should be avoided during pregnancy.
- Aminoglycosides can be considered if the benefit to the mother is felt to outweigh the risk to the mother.
- Discussion with the microbiology team is advised.

Cardiac drugs in pregnancy

- This section provides a summary of some important cardiac drugs to be used or avoided during pregnancy.
- Several databases are available and recommended by the ESC as an appropriate source of additional information.
- Data regarding safety in pregnancy and breastfeeding are often limited. Clinicians are advised to look up medications in appropriate pharmacological resources before prescribing if in doubt.

Pharmacokinetics during pregnancy

- Drug pharmacokinetics can change significantly during pregnancy.
- CV effects are outlined in ➔ Physiological changes in pregnancy, pp. 392–3. Additionally, there are changes in liver enzymes, delayed gastric emptying, vomiting, and ↑ glomerular filtration, which can alter drug absorption/metabolism/excretion.

Anticoagulants

- These are discussed in detail in Box 9.7.

β-blockers

- Generally safe in pregnancy.
- Associated with ↑ rates of fetal growth restriction.

- β1-selective agents preferred due to reduced effects on uterine contraction and peripheral vasodilatation.
- Unselective agents have significantly higher rates of fetal growth restriction.
- Labetalol is recommended for treatment of hypertension in pregnancy.

Calcium channel blockers

- CCBs may be associated with ↑ risk of neonatal seizures.
- Diltiazem is teratogenic in animals and should be avoided.
- Verapamil is considered relatively safe in pregnancy and is considered an appropriate treatment for AF or idiopathic VT during pregnancy.

Renin–angiotensin–aldosterone system inhibitors

- Both ACEis and ARBs are teratogenic and must be avoided.
- Spironolactone is not advised during pregnancy.
- Eplerenone is associated with post-implantation losses in animal models and should similarly be avoided.

Statins

- It is advised that statins are not prescribed during pregnancy or breastfeeding.
- Little evidence exists regarding their safety during pregnancy.
- No difference in the rate of birth defects in mothers taking statins.

Further reading

Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, *et al.* 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;**39**:3165–241.

Chapter 10

Multisystem disorders

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Coronary artery disease in patients with rheumatological diseases

- CVD is a significant cause of morbidity and premature death in patients with rheumatic diseases.
- Traditional atherogenic risk factors are often over-represented in rheumatic diseases but do not fully account for ↑ CV risk.

Inflammation and atherogenesis

- Inflammation is fundamental to the initiation and progression of atherosclerosis (see Table 10.1).
- Lipid-laden macrophages within atherosclerotic plaques are a source of several inflammatory mediators.
- Cytokines such as TNF-α and IL-1β have a range of atherogenic effects on endothelial function and leucocyte recruitment and proliferation, and promote reactive oxygen species.
- High-sensitivity CRP is a marker of systemic inflammation which, while not causal, is consistently associated with ↑ CV risk.

Anti-inflammatory therapies and cardiovascular risk

- *Canakinumab:* blockade of IL-1β ↓ CV death, non-fatal MI, and stroke by 15% in patients with previous MI (CANTOS trial).
- *Colchicine:* ↓ ischaemic events in patients with stable CAD and with recent MI (COLCOT trial).
- *Corticosteroids:* exacerbates conventional risk factors such as hyperlipidaemia, hypertension, and insulin resistance.

Epidemiology

Systemic lupus erythematosus

- The prevalence of subclinical IHD is not known; however, those with SLE are 5–10 times more likely to have an MI than the general population.

Rheumatoid arthritis

- MI incidence of 4.8–5.9/1000 person-years in those with RA. Patients with RA are 2–3 times more likely to have an MI than matched controls.
- NICE recommends annual CV risk assessments in patients with RA.
- ↑ disease activity confers ↑ CV risk, and aggressive treat-to-target approaches are shown to ↓ events.
- Validated population CV risk estimators are recognized to under- (Framingham) or overestimate (QRISK®2) risk in RA.

Table 10.1 Cardiac manifestations of rheumatic diseases

	Pericardial disease	Myocardial disease	Valvular disease	Aortic root disease	Coronary disease	Conduction system disease
Ankylosing spondylitis	+	+	++	++		+
Behçet's disease	+		+	+	+	
Eosinophilic granulomatosis with polyangiitis	++	+	+		+	+
Giant cell arteritis		+	+	++	+	
Granulomatosis with polyangiitis	+		+		+	
Kawasaki disease	+	++	+		+++	
Neonatal lupus erythematosus		+				++
Polyarteritis nodosa					++	
Polymyositis/ dermatomyositis	+	++				+
Reiter's syndrome			+			
Rheumatoid arthritis	+++	+	+	+	++	
Still's (adult) disease	++	+		+		+
Systemic lupus erythematosus	+++	+	++	+	++	+
Systemic sclerosis	++	++			+	++
Takayasu's arteritis	+	+	++	+++	+	+

Source: data from Watts RA *et al*. *Oxford Textbook of Rheumatology* (2018).

Rheumatoid arthritis

- RA is a multisystem autoimmune disease characterized by symmetrical, erosive inflammatory polyarthritis.

Epidemiology

- UK prevalence is ~1%; ♂:♀ 1:3.
- Seropositivity for RF and anti-CCP antibody confers risk of aggressive erosive arthritis and extra-articular disease.
- Major risk factors are genetic (HLA-DRB1 alleles) and smoking.

Clinical features

Arthritis

- Can involve any synovial joint, but particularly the wrists and small joints of the hands and feet.
- Classically associated with prolonged early morning joint stiffness.
- Progressive erosive arthritis leads to joint deformity and disability.

Extra-articular features

- *Constitutional symptoms:* such as fever, malaise, and fatigue.
- *Rheumatoid nodules:* are most commonly subcutaneous but can affect any organ, predominantly in smokers with seropositive disease.
- *Lung disease:* includes nodules, pleuritis and effusions, bronchiectasis, small airways obstruction, and interstitial lung disease.
- *Osteopenia:* prominent with accelerated fracture risk.
- *Eye involvement:* includes scleritis, episcleritis, and sicca syndrome.
- *Vasculitis:* serious complication of RA affecting small and medium-sized vessels; 1–5% of those with RA. Can involve coronary arteries.
- *Anaemia:* common and multifactorial.

Investigations

- If RA is suspected, RF and anti-CCP antibodies should be tested.
- X-ray imaging of hands and feet in those with suspected RA to assist with diagnosis and assess for erosions.
- US imaging of joints is widely used and may detect synovitis and/or early joint erosions.

Cardiovascular involvement

Coronary artery disease

- See ➔ Coronary artery disease in patients with rheumatological diseases, p. 428.

Pericarditis

- Most common CV complication of RA (30–50% of those with RA have some pericardial involvement). More common in men.
- Fifty per cent of cases have benign fibrinous pericarditis, with effusions seen in 40% of cases on echocardiography.
- One to 2% of those with RA are symptomatic.
- Usually independent of disease duration and may precede it.
- Cardiac tamponade and constrictive pericarditis are rare.
- Responds to treatment with steroids and disease-modifying drugs.

Myocardial and endocardial granulomas

- Relatively common among patients with subcutaneous nodules.
- Typically subclinical but rarely cause compromise through MV deformity and MR.
- Rarely, they cause conduction problems, most commonly first-degree heart block, but also LBBB or CHB.

Myocarditis

- Twenty per cent of patients with severe RA have diffuse myocarditis, with non-specific inflammatory infiltrates, myocyte necrosis, and fibrosis.
- Can cause HF, arrhythmias, and abnormal conduction.
- Ventricular function may also be ↓ by secondary amyloidosis.

Valvular disease

- Non-specific valvulitis produces fibrotic, hyalinized valves with incompetence. Aortic valve more commonly than MV.

Treatment

- Early intensive treatment targeting remission or low disease activity prevents joint damage and disability, and reduces systemic complications, including CVD.
- Should aim for remission or low disease activity.
- *Disease-modifying anti-rheumatic drugs (DMARDs):* should be initiated early. Methotrexate, leflunomide, or sulfasalazine are first line.
- *Biologic agents:* early escalation should be prompted by active disease despite DMARD use. These are prescribed in specialist clinics. Biological therapies include:
  - TNF-α inhibitors: adalimumab, etanercept, infliximab
  - IL-6 inhibitors: tocilizumab, sarilumab
  - Janus kinase (JAK) inhibitors: baricitinib
  - Anti-CD20: rituximab
  - IL-1 receptor antagonists: anakinra, canakinumab.

Rheumatoid arthritis predictors of coronary artery disease

- Older age at disease onset
- Early corticosteroid therapy
- Long-standing disease (>10 years)
- Active extra-articular disease
- Active erosive and nodular disease
- Vasculitis
- High serum titres of rheumatoid factor or haptoglobin
- Erythrocyte sedimentation rate >55mm/h

Systemic lupus erythematosus

Epidemiology

- Multisystem autoimmune rheumatic disease.
- ♀:♂ 9:1. Peak onset in second and third decades.
- Prevalence varies by ethnicity and geography. Higher incidence among those of Asian or Afro-Caribbean ancestry and Hispanics, compared with those of white ancestry, in both Europe and America.

Clinical features

- *Mucocutaneous involvement:* photosensitivity, inflammatory rashes, oral ulcers.
- *Arthritis:* generally symmetric polyarthritis, commonly in the knees, shoulders, wrist, and small joints of the hand. Some develop a deforming non-erosive arthropathy.
- *Haematological disease:* haemolytic anaemia, leucopenia, thrombocytopenia.
- *Renal disease:* lupus nephritis.
- *Neurological:* neuropsychiatric disease.
- *Antiphospholipid syndrome (APS):* a secondary form of this condition may complicate SLE.
- *Lung disease:* pleuritis—most common respiratory manifestation of SLE. Pleuritic pain present in 45–60% of those with SLE. Pneumonitis seen in ~10% of patients.

Investigations

Immunological abnormalities

- Characterized by ANA.
- *Anti-Sm and anti-dsDNA:* highly specific for SLE.
- *Complement:* levels fall in active disease.

Cardiovascular involvement

Coronary artery disease

- Associated with accelerated atherosclerosis (see ➲ Coronary artery disease in patients with rheumatological diseases, p. 428).

Pulmonary hypertension

- PHT may occur, though more frequently in scleroderma and mixed connective tissue disease (MCTD) (see ➲ Pulmonary hypertension and rheumatic diseases, p. 442).

Pericarditis

- Serositis involving the pleura and pericardium is symptomatic in ~25% of those with SLE at some point in their disease.
- Subclinical pericardial effusion is common.
- Pericardial fluid is usually exudative.
- Frequently associated with active disease in other organs, so full assessment of disease activity is required.
- Unlike other manifestations of SLE, serositis is associated with high CRP level. Fever or constitutional upset is common.
- Complications such a tamponade and constrictive pericarditis are rare but can occur; invasive therapy is not usually required.
- Typically responsive to steroid therapy. Escalation of other disease-modifying therapy may be warranted.

Myocarditis

- Myocarditis is a vasculopathy rather than true myositis; creatine kinase (CK) level is usually normal.
- For clinical features and diagnostic criteria of myocarditis, see ➔ Myocarditis: aetiology and clinical features, p. 286.
- May be complicated by development of HF.
- Clinically apparent disease usually requires corticosteroid therapy and immunosuppression (such as cyclophosphamide), in addition to standard HF therapy.

Cardiomyopathy

- Generally uncommon, with clinically apparent cardiomyopathy in ~10% of those with SLE. Subclinical findings more common.

Valvular heart disease

- *Epidemiology:* found in 28–74%.
- *Most common valve involvement:* MV followed by aortic valve. Other valves and endocardial surfaces may also be affected. It may cause valve regurgitation; stenosis is rare.
- *Libman–Sack's (marantic) endocarditis:* occurs in 4–43% of those with SLE; it is more frequently associated with antiphospholipid antibodies. Valve leaflet thickening occurs in 19–52% of those with SLE, with associated regurgitation in 73%.

Conduction defects

- Conductions abnormalities can be detected in up to 5% of patients.
- Arrhythmia may be a sequela of active or previous myocarditis.

Treatment

- *Corticosteroids:* frequently used for rapid disease control and tapered.
- *Hydroxychloroquine:* often sufficient for mild disease and reduces flares. Also has protective effect on CV outcomes, pregnancy morbidity, and overall mortality. ↓ organ damage accrual. Requires monitoring for retinal toxicity with prolonged use. Hydroxychloroquine ↑ QT interval in some individuals and ↑ arrhythmic risk. Rarely can lead to LV systolic dysfunction.
- *Immunosuppressive agents:* principally azathioprine, methotrexate, and mycophenolate mofetil. Choice of agent is guided by disease severity and organ system involvement.
- *B cell depletion:* using rituximab and belimumab, the latter an anti-B cell-activating factor monoclonal antibody, are reserved for resistant disease.

Antiphospholipid syndrome

- APS is an acquired autoimmune thrombophilia, characterized by arterial and venous thrombosis and/or obstetric morbidity.

Epidemiology

- It may be a primary disorder or associated with autoimmune rheumatic disease, specifically SLE in 35%.
- Incidence of 2–5 cases per 100,000 person-years.

Clinical features

- *Venous thromboses:* more common than arterial events.
- *Obstetric complications:* include early pregnancy loss, pre-eclampsia, placental insufficiency, and intrauterine growth restriction.
- *Other features:* include thrombocytopenia and livedo reticularis.
- *Catastrophic APS:* life-threatening, rapidly evolving multiorgan dysfunction with microthromboses and antiphospholipid antibodies.

Investigations

- *Immunology:* lupus anticoagulant or antiphospholipid antibodies (anticardiolipin and anti-β_2-glycoprotein), and clinical features, should be detected ≥2 occasions 12 weeks apart for diagnosis
- *Thrombotic risk:* triple-positive APS (anticardiolipin, anti-β_2-glycoprotein and lupus anticoagulant) confers ↑ thrombotic risk.

Cardiovascular involvement

Valvular disease

- *Epidemiology:* valve abnormalities are found in 30–40% of cases, particularly those with peripheral arterial thromboses. Vegetations occur in 6–10% and thickening in 10–24%.
- *Most common valve involvement:* as with SLE, the MV is most frequently affected, followed by the aortic valve.
- *Treatment:* there is no evidence that immunosuppression or anticoagulation reduces the risk of valve involvement.

Thrombotic disease

- *MI:* may occur due to primary thrombotic disease despite normal angiography; ~10% of patients with MI have antiphospholipid antibodies.
- *PHT:* may result from PE and pulmonary veno-occlusive disease.
- *Cardiomyopathy:* may occur as a result of thrombi, leading to micro-angiopathic cardiomyopathy.

Treatment

- Should be individualized to thrombotic risk. Those with positive antibodies, but no symptoms/thromboses, do not require treatment.
- ↓ other thrombotic risk factors (oral contraceptives, smoking, etc.).
- In those with thrombosis, warfarin should be initiated (target INR 2–3) for ≥3 months. Total duration should be individualized.
- DOACs are not recommended for secondary prevention.

Sjögren's syndrome

- Condition characterized by autoimmune lymphocytic destruction of exocrine glands, causing sicca syndrome—for example, lymphocytic infiltration of the salivary and lacrimal glands lead to dry eyes and mouth.

Epidemiology

- It may develop secondary to other autoimmune disease such as RA or SLE.
- Primary Sjögren's syndrome (SS) affects younger patients and is associated with greater extra-glandular and systemic features.
- More common in women than in men and may affect ≤3% of individuals.

Clinical features

- Key features are dry mouth and dry eyes.
- Other extra-glandular features are common, involving multiple organ systems, including renal tubular acidosis, vasculitis, lymphoma, anaemia, and pulmonary fibrosis.
- Raynaud's phenomenon is common.
- Arthralgia commonly coexists.

Investigations

- *Immunology*: anti-Ro/SSA (50% of cases) and anti-La/SSB (40–50% of those with SS) antibodies are a hallmark of the disease. However, also relatively common in those without SS. RF may also be positive.
- *Schirmer's test:* a strip of filter paper is placed inside the lower eyelid for 5min; <5mm of liquid is suggestive of SS.
- *Sialography:* a contrast agent is injected into the salivary glands. SS shows diffuse obstructions (but non-diagnostic).
- *Biopsy:* salivary gland biopsy and histopathological assessment are diagnostic, but often not required.

Cardiovascular involvement

- Clinically apparent cardiac disease is rare in SS, though subclinical pericarditis, pericardial effusion, diastolic dysfunction, and PHT are described.

Treatment

- There are no disease-modifying therapies at present and treatment is principally symptomatic.
- Artificial tears and saliva are the mainstay of treatment.
- Paracetamol and NSAIDs often used to treat arthralgia.
- Immunosuppressive agents (e.g. intermittent short courses) can be considered for systemic flares or in significant organ manifestations.

Neonatal lupus

- Neonatal lupus is associated with transplacental transmission of maternal anti-Ro/SSA antibodies and anti-La/SSB antibodies, which are characteristic of SS but may also be positive in SLE and other autoimmune rheumatic diseases.

Epidemiology

- Congenital heart block affects 1–2% of anti-Ro/SSA or anti-La/SSB-positive pregnancies.
- ↑ risk of cardiac and cutaneous features in ♀ (2–3:1), compared with ♂ children.

Clinical features

- The major manifestations are cardiac and cutaneous.
- *Neonatal cutaneous lupus erythematosus:* most commonly a self-limiting photosensitive rash during the first 2 months of life.
- *Other features:* may include transient cytopenia, haemolysis, or deranged liver function.

Congenital heart block

- *Features:* significant second/third-degree heart block presenting as fetal bradycardia typically in a structurally normal heart.
- *Incidence:* accounts for 80–90% of congenital heart block detected *in utero* or during the neonatal period.
- *High-risk period:* heart block generally develops between 18 and 25 weeks' gestation.
- *Recurrence:* after one affected pregnancy, the risk in subsequent pregnancies is ~17%.
- *Outcome*: second-degree block may spontaneously revert to SR, but CHB leads to fetal loss in 10–20% and is generally irreversible.
- *Surveillance:* widely used in anti-Ro/La-positive pregnancies by using fetal echocardiography.
- *Avoidance:* some evidence suggests systemic corticosteroids may prevent cardiac manifestations. Retrospective data suggest maternal treatment with hydroxychloroquine may be protective *in utero* and ↓ recurrence after one affected pregnancy.
- *Treatment:* if CHB develops, a pacemaker is usually required.

Other cardiovascular involvement

- Myocarditis and pericarditis are recognized.
- Endocardial fibroelastosis can result in cardiomyopathy, HF, and VHD.

Systemic sclerosis

- Systemic sclerosis is an autoimmune rheumatic disease characterized by microvascular dysfunction, inflammation, and fibrosis in the skin and other internal organs.

Epidemiology

- Generally rare, with an incidence of 3.7–23 per million in European populations.
- More common in women than in men (3:1).
- Normally develops in women aged 30–40 years.

Clinical features

- *Limited cutaneous systemic sclerosis:* scleroderma is confined to the face and distal limbs; associated with anti-centromere antibodies; commonly involves Raynaud's phenomenon, digital ulcers, calcinosis, GI dysmotility, and mucocutaneous telangiectasia.
- *Diffuse cutaneous systemic sclerosis:* more rapidly progressive and widespread scleroderma; associated with Scl-70 antibodies; higher risk of interstitial lung disease and hypertensive renal crisis.

Investigations

- Ninety per cent of cases have ANA.
- Anti-centromere antibodies substantially more common in the limited form.
- Anti-Scl-70 antibodies often found in the diffuse form (30–40%).

Cardiovascular involvement

- Frequently under-recognized, but associated with ↑ morbidity/mortality.
- *Microvascular coronary vasculopathy:* leads to recurrent ischaemia, inflammation, and myocardial remodelling and fibrosis, which may be evident on CMR.
- *Diastolic dysfunction:* ↑ myocardial thickness is associated with diagnostic dysfunction, which is more common than systolic dysfunction.
- *Conduction defects:* conduction block may be present in up to 15% of those with systemic sclerosis but may require prolonged monitoring to be diagnosed.
- *Arrhythmias:* two-thirds of patients develop supraventricular arrhythmias.
- *Pericardial disease:* may develop fibrinous or fibrous pericarditis and/or pericardial effusion. May be more common in those with limited form (~30%), compared with those with the diffuse form (~15%). Often asymptomatic.
- *RV dysfunction:* may result from pulmonary arterial hypertension (PAH) (see ➔ Pulmonary hypertension and rheumatic diseases, p. 442) or LV dysfunction. PHT is the leading cause of death in patients with systemic sclerosis.

Treatment

- Treatment depends on the form of systemic sclerosis and disease form.
- *Raynaud's:* CCBs (first line), tadalafil, and bosentan are often used. IV prostanoids may be used in severe cases.
- *Renal involvement:* treatment with ACEis (or ARBs).
- *PHT* (see ➔ Pulmonary hypertension and rheumatic diseases, p. 442).

Hypertensive renal crisis

- This affects 10–15% of patients with diffuse cutaneous systemic sclerosis and typically occurs early in the disease.
- May be the first manifestation of systemic sclerosis.

Clinical features

- Scleroderma renal crisis presents with severe or accelerated hypertension and acute kidney injury with microscopic haemoproteinuria.

Pathogenesis

- Activation of the renin–angiotensin–aldosterone axis is central to the pathogenesis.
- Scl-70 and RNA polymerase III antibodies confer the highest risk.

Potential outcomes

- Hypertensive encephalopathy, pulmonary oedema, left ventricular failure, and tachyarrhythmia can ensue.
- Microangiopathic haemolytic anaemia is frequently seen.

Management

- Close supportive care and blood pressure lowering are critical.
- For emergency management of hypertension, see ➔ Malignant hypertension, p. 846.
- Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are first line and are prognostically beneficial for renal recovery, even among patients who are initially dialysis-dependent.

Ankylosing spondylitis

Epidemiology

- Prevalence varies by ethnicity; 1% among Caucasians; ♂:♀ = 2:1. Onset at age under 40 years.
- HLA-B27 accounts for 50–90% of the risk; 1–2% of those who are HLA-B27-positive develop AS.

Clinical features

- *Back pain:* insidious inflammatory type, relieved by exercise with marked morning stiffness. Alternating buttock pain suggests sacroiliitis. Spinal restriction accrues over time.
- *Peripheral musculoskeletal:* peripheral involvement (arthritis and enthesitis) in 30–50% of those with AS. Hip (25–30%), shoulders, and chest wall joints commonly involved. Other common sites: Achilles tendon insertion, plantar fascia, and tibial tuberosity.
- *Complications:* include spinal deformity, chest wall restriction, and neurological deficits resulting from ankylosis or fractures.
- *Extra-articular features:* uveitis (25–30% cases), psoriasis (10%), and inflammatory bowel disease (≤60%), which may be subclinical. Bilateral apical lung fibrosis is uncommon.

Investigations

- *Blood tests:* ESR/CRP ↑, alkaline phosphatase (ALP) ↑ in 50%. Occasionally normocytic anaemia.
- *Plain radiographs:* lack sensitivity in early disease, but serial assessment of sacroiliac joints can be useful for ongoing disease evaluation.
- *MRI:* active sacroiliitis is detected on MRI as bone marrow oedema seen on T2 STIR (short tau inversion recovery) or T1 fat-suppressed sequences. Erosions and sclerosis indicate established disease. Squared-off vertebral bodies and syndesmophytes culminate in bamboo spine. Fatty deposition at vertebral corners on MRI is detected earlier.

Cardiac involvement

- Significantly associated with HLA-B27 positivity.
- *AR:* 1–10% of those with AS. Due to sclerosing ascending aortitis (1–10% cases) or aortic valve fibrosis causing cusp thickening, nodularity, and shortening.
- *Conduction defects:* most commonly AVN disease and CHB.
- *Anterior MV leaflet thickening:* rarely causes MR.
- *Myocardial fibrosis:* results in systolic and diastolic dysfunction. May progress to DCM. Fibrosis of the aortic valve and MV junction producing subaortic bump on echocardiography.
- *Pericarditis:* <1% of cases.

Treatment

- Exercise and focused physiotherapy.
- *NSAIDs:* sufficient to manage milder, non-progressive disease.
- *Biologic therapy:* includes anti-TNF-α agents (infliximab), anti-IL-17A (secukinumab), and anti-IL-12/23 (ustekinumab).
- *Corticosteroids:* systemic administration should be avoided. However, local use in patients with active enthesitis (should avoid peri-tendon injection of the Achilles, patella, and quadriceps).

Immunoglobulin G4-related disease

- Immunoglobulin G4 (IgG4)-related disease is an autoimmune-mediated chronic inflammatory condition.
- This condition was first described in 2003.
- The underlying pathophysiology is related to IgG4-positive plasma cells in affected tissues, resulting in chronic inflammation and fibrosis.

Epidemiology

- The incidence and prevalence of this condition are not well established.
- More common in men (♂:♀ = 1.6:1).

Clinical features

- IgG4-related disease is characterized by a relapsing–remitting course, with mass-forming lesions in multiple sites.
- Clinical manifestations principally depend on the organ sites involved. Common organ systems include brain, eye, heart, lungs, GI tract, and kidneys.
- Autoimmune pancreatitis is common.

Investigations

- Definitive diagnosis can be difficult.
- *Biopsy:* principally mechanism based on tissue biopsy of an affected organ. Staining for IgG+ cells by using either IgG or CD138 staining.
- *CRP/ESR:* may be normal or mildly elevated. Substantially elevated CRP or ESR may suggest an alternative diagnosis (e.g. ANCA-associated vasculitis).
- *Serum IgG4:* elevated in >50% of cases, but normal levels do not exclude diagnosis.
- Other investigations will depend on tissue involvement.

Cardiovascular involvement

- The epidemiology of CV involvement in IgG4-related disease is not well established.
- *Aortitis:* IgG4-related aortitis is recognized.
- *CAD:* stenosis may occur as a result of mass formation surrounding the artery or periarterial inflammation of the coronary arteries. May result in myocardial ischaemia/MI.
- *Pericardium:* pericarditis, pericardial thickening, and effusion are all recognized with IgG4+ plasma cells identified in biopsy specimens.

Treatment

- The aim of treatment is to induce remission to prevent tissue fibrosis.
- *Corticosteroids:* systemic steroid therapy is the cornerstone of therapy in IgG4-related disease.
- Evidence for steroid-sparing agents is currently lacking.

Pulmonary hypertension and rheumatic diseases

WHO classification of pulmonary hypertension

Group 1: pulmonary arterial hypertension

Subclassification includes idiopathic, heritable, drug/toxin-induced, and subsets of underlying systemic diseases

Group 2: pulmonary hypertension with left heart disease

Group 3: pulmonary hypertension associated with lung disease and/or hypoxia

Group 4: chronic thromboembolic pulmonary hypertension and other pulmonary artery obstruction

Group 5: pulmonary hypertension of unclear and/or multifactorial mechanisms

Source: data from Simonneau *et al*. *J Am Coll Cardiol*. 2009;**54**(1):S43–54.

- PHT in autoimmune connective tissue diseases (CTDs) comprises group 1, group 2, and group 3 subsets, which may coexist.
- PAH (group 1) is the leading cause of death in systemic sclerosis and affects 10–15%. Those with long-standing limited cutaneous systemic sclerosis with anticentromere antibodies.
- PAH is well recognized in MCTD, SLE, and less frequently in RA, dermatopolymyositis, and SS.
- Survival in CTD or rheumatic disease-associated PAH is significantly lower than in idiopathic PAH.
- Active annual screening of at-risk asymptomatic patients is advocated by using a combination of pulmonary function tests, echocardiography, and biomarkers.
- Reduced or declining gas transfer (DLCO) with preserved lung volumes may signify subclinical PAH. High-resolution CT is useful to assess for the presence or extent of concurrent interstitial lung disease.
- Definitive diagnosis using right heart catheterization and pulmonary vasodilator treatment should be directed by a specialized centre.
- Specific drug therapy includes CCBs (nifedipine, diltiazem), endothelin receptor antagonists (bosentan, ambrisentan, macitentan), and phosphodiesterase inhibitors (sildenafil, tadalafil), but the magnitude of treatment response is consistently lower in CTD-PAH than in idiopathic disease.
- IV prostacyclin analogues (iloprost, epoprostenol) may be favoured where there is severe concurrent digital vasculopathy and ulceration.
- Immunosuppression using systemic corticosteroids and cyclophosphamide may yield clinical improvement in PAH among patients with SLE and MCTD.

Polymyositis and dermatomyositis

- Idiopathic inflammatory myopathies, including polymyositis (PM) and dermatomyositis (DM), are a diverse group of disorders characterized by immune-mediated muscle inflammation leading to painless proximal muscle weakness.

Epidemiology

- Peak age of onset 40–50 years; more common in women.

Clinical features

- *Polymyositis:* presents with weakness, pain, and loss of muscle mass in proximal muscle groups.
- Dysphagia is common (~30% of patients).
- *Dermatomyositis:* additionally presents with stereotyped cutaneous findings (heliotrope rash, Gottron's papules, shawl sign), which are worsened in sunlight exposure.
- Associated with a higher risk of cancer.

Investigations

- *Muscle biopsy:* gold standard for a definitive diagnosis.
- *MRI:* demonstrates characteristic findings of myositis; can be used to aid in diagnosis and guide muscle biopsy.
- *EMG*: both PM and DM demonstrate prominent muscle membrane irritability in proximal muscles.
- *Muscle enzymes:* elevated muscle enzymes (CK, AST, LDH) and the presence of myositis-specific antibodies are supportive of the diagnosis.
- *Myositis-specific antibodies:* present in ~20% of cases and correlate with distinct clinical disease patterns, particularly extra-muscular manifestations such as skin rashes, interstitial lung disease, and malignancy.

Cardiovascular involvement

- Excess cardiac mortality in PM and DM reflects both primary cardiac involvement and accelerated CV risk associated with chronic inflammation.
- Primary inflammatory cardiac involvement occurs in up to 75% of patients with myositis but is frequently subclinical.
- *Troponins:* cardiac troponins may be elevated in active myositis due to release from damaged and regenerating skeletal muscle. Cardiac troponin I correlates most strongly and specifically with cardiac involvement.
- *Arrhythmias:* ECG and Holter monitoring may be abnormal in over 70%, most frequently with prolonged conduction intervals and atrial arrhythmias.
- *Myocarditis:* inflammation and fibrosis may be detected by CMR, LGE, and diastolic dysfunction. Evidence of overt myocarditis should prompt escalation of immunosuppressive therapy.

Treatment

- First-line therapy is with corticosteroids.
- Additional immunosuppressive therapy (e.g. azathioprine, methotrexate, IVIg, or cyclophosphamide) may be required in patients with insufficient response to steroids (or as steroid-sparing agents).
- Rituximab may be used in treatment-refractory patients.

Vasculitides: giant cell arteritis

- Involves granulomatous inflammation of medium-sized to large arteries.

Epidemiology

- It is the most common systemic vasculitis. UK incidence ~20 per 100,000; peak onset age 70–80 years, exceptionally rare at age <50 years. More common in women than in men (2:1) and in those of northern European origin.

Clinical features

- Temporal headache and scalp tenderness.
- Jaw claudication.
- Constitutional upset.
- Stiffness and pain in neck/shoulders/upper arms/hips—polymyalgia rheumatica present in ~50% of those with giant cell arteritis (GCA).
- Sudden visual loss due to ocular ischaemia is largely irreversible.

Investigations

- *ESR/CRP:* typically raised in active disease.
- *Temporal artery biopsy:* gold standard for determining a definitive diagnosis. However, GCA often has skip lesions.
- *Temporal artery US:* increasingly adopted and detects a characteristic halo sign surrounding inflamed vessels.

Cardiac complications

Aortitis

- Prevalent in GCA, but mostly subclinical.
- FDG-PET identifies active inflammation in vessel wall. Mural thickening and aneurysm can be seen by MRA and CT angiography.
- Aortitis in GCA is complicated by aortic dissection in 1–5%, aortic root dilatation leading to aortic valve incompetence, and aneurysms predominantly in the thoracic aorta in 8–10%.

Treatment

- *Corticosteroids:* first-line therapy is high-dose corticosteroids. Steroid weaning can be prolonged and requires specialist involvement.
- *DMARDs* (e.g. methotrexate): may have a steroid-sparing role.
- *Cyclophosphamide:* may be used for extensive large-vessel disease.
- *Tocilizumab:* an anti-IL-6 receptor monoclonal antibody, approved for use in refractory disease.

Vasculitides: Takayasu arteritis

- This is a rare granulomatous, large-vessel vasculitis involving the aorta and its primary branches.

Epidemiology

- Rare condition, with a prevalence 3–6 per million people.
- Predominantly affects women (~80%), with onset under the age of 40 years.
- Worldwide distribution, with greater frequency in East Asia, the Middle East, and Central/South America.
- Inflammatory infiltrates causing focal arterial stenosis or occlusion are characteristic.

Clinical features

- Initial inflammatory phase characterized by fever, weight loss, myalgia, and arthralgia are common.
- Subsequent 'pulseless' phase results in symptoms secondary to vascular insufficiency: acute stroke, abdominal pain, limb claudication, and asymmetrically diminished peripheral pulses/BP.
- Syncope can occur and be the result of subclavian steal or carotid sinus hypersensitivity.

Investigations

- *CT angiography or MRA:* will demonstrate vascular lesions in large/medium-sized vessels. Can be divided into one of six types, based on angiographic findings.
- *FDG-PET:* will show features of active vascular inflammation.
- *Vascular US:* diffuse arterial wall thickening (macaroni sign).
- Tissue biopsy plays no significant role in the diagnosis of Takayasu arteritis.

Cardiovascular involvement

- *Hypertension:* often reflects renal artery stenoses and can precipitate HF.
- *AR and angina:* may complicate aortitis of the aortic root. AR seen in ~20% of those with Takayasu arteritis.
- Pericarditis, CCF, and MI are recognized, but uncommon.

Treatment

- Medical therapy is based on immunosuppression. Initial therapy is with corticosteroids.
- Additional adjunctive therapy is recommended with methotrexate or mycophenolate mofetil.
- TNF-α inhibitors or tocilizumab can be considered in relapses.
- Balloon angioplasty, stenting, or bypass surgery may be considered, but restenosis is not infrequent.

Vasculitides: Kawasaki disease

Epidemiology

- The second most common childhood vasculitis, after immunoglobulin A (IgA) vasculitis.
- Incidence varies geographically; ↑ in East Asia and among those of Asian ancestry. Onset <5 years in 80–90%. Boys ↑ affected (2:1).
- There is large/medium-sized arteritis, particularly the coronary arteries.

Clinical features

(See Box 10.1)

- Typically, a self-limiting febrile illness lasting ~12 days.

Investigations

- *Blood tests:* there are no specific laboratory investigations for KD; however, CRP/ESR ↑. FBC will demonstrate normocytic anaemia ± thrombocytosis. LFTs demonstrate ↑ alanine aminotransferase (ALT) and ↓ albumin.
- *Urinalysis:* may demonstrate pyuria and proteinuria.
- *ECG:* may show prolonged conduction intervals, ST-segment and T wave abnormalities, or Q waves. Significant arrhythmia suggests ischaemia.
- *Echocardiography:* all affected children should have serial echocardiography to detect coronary aneurysms at diagnosis and in the convalescent phase at 2 weeks and 6–8 weeks after onset.
- *CT angiography and MRA:* may provide high-resolution coronary imaging, particularly for more distal aneurysms.
- Stress testing, spiral CT, and/or cardiac MRI may be required to assess for, or monitor, disease. Coronary angiography is rarely used diagnostically and is reserved for cases of coronary artery aneurysms.

Box 10.1 Diagnostic criteria for Kawasaki disease

Fever persisting for ≥5 days and ≥4 of the following features:

- Changes in extremities:
  - *Acute*: erythema and oedema of hands/feet
  - *Subacute*: membranous desquamation of fingertips and periungual peeling
- Polymorphous exanthema.
- Bilateral, painless bulbar conjunctival injection without exudate.
- Changes in lips/oral cavity: erythema and cracking of lips, strawberry tongue, diffuse injection of oral/pharyngeal mucosae.
- Cervical lymphadenopathy (>1.5cm).

Reproduced from Newburger et al. Circulation. 2004;110:2747–71 with permission from Wolters Kluwer Health Inc.

Cardiovascular involvement

Coronary artery aneurysms

- The most significant complication and may lead to ischaemia, MI, and sudden death.

- Develop in ≤25% if untreated; infants <6 months at ↑ risk; ~20% develop transient proximal LAD/RCA aneurysms, even if treated.
- Proximal LAD and RCA are most affected.
- Onset is from the second week of illness; enlarge over 4–6 weeks from onset. Giant aneurysms develop in 1%.
- Spontaneously resolution in ~50% to normal calibre over 2 years.
- Risk of MI is highest in the first 12 months, but excess risk and accelerated atherosclerosis persist into adulthood.

Other cardiac involvement

- *Myocarditis:* most common non-coronary complication; present in 50–70% of patients and develops in the acute phase.
- *Ventricular dysfunction:* mild to moderate dysfunction is seen in 25–50%; may be associated with gallop rhythm.
- *MR:* develops in ~25% during acute illness.
- *Pericardial effusions:* can develop; are usually small.

Treatment

Acute therapy

- *IVIg:* single dose of 2g/kg given over 10–12h; ↓ risk of coronary aneurysms to <5% if commenced within 7–10 days of fever onset. Treatment later than day 10 is still indicated if systemic inflammation persists.
- *Aspirin:* 30–100mg/kg daily initiated early; does not ↓ coronary artery aneurysms. Once afebrile for 48–72h, continued at ↓ dose for 4–6 weeks until no coronary abnormalities detected. In those with coronary aneurysms, aspirin may be continued indefinitely.

Subacute therapy

- Non-acute therapies depend on the presence of coronary abnormalities, which also determine cardiology follow-up duration and frequency.
- *Antiplatelet therapy:* long-term single- or dual-agent therapy is considered if medium to large coronary aneurysms persist.
- *Anticoagulation:* warfarin, in addition to antiplatelets, should be considered if giant aneurysms are detected.
- *Corticosteroids/anti-TNF-α therapy:* both options for resistant cases.
- *Coronary revascularization:* in a minority of patients, CABG/PCI is indicated for coronary thrombosis/stenosis or acute MI.
- *Valvular surgery:* occasionally required.

Differential diagnosis of Kawasaki disease: diseases and disorders with similar clinical findings

- Coronavirus disease 2019 (see ➔ Coronavirus disease 2019, pp. 452–3)
- Viral infections (particularly measles)
- Scarlet fever
- Staphylococcal scalded skin syndrome
- Toxic shock syndrome
- Bacterial cervical lymphadenitis
- Drug hypersensitivity reactions
- Stevens–Johnson syndrome
- Juvenile rheumatoid arthritis
- Rocky Mountain spotted fever
- Leptospirosis
- Mercury hypersensitivity reaction (acrodynia)

Vasculitides: ANCA-associated vasculitis

These are systemic small/medium-sized vessel necrotizing vasculitides associated with ANCA-recognizing proteinase 3 (PR3) and MPO.

Eosinophilic granulomatosis with polyangiitis

- Previously known as Churg–Strauss syndrome.

Epidemiology

- This condition is rare, with 2–3 cases per 100,000 adults/year.
- Slightly ↑ in men vs women, with a typical onset at age 40–50 years.

Clinical features

- Prodromal phase of atopy, late-onset asthma, rhinosinusitis, and nasal polyposis, followed by a vasculitic phase with eosinophilia.
- Major organ involvement includes eosinophilic pulmonary infiltrates, peripheral neuropathy, mononeuritis multiplex, and renal insufficiency.

Investigations

- *ANCA:* positive in 30–60%, usually MPO.
- *FBC:* normally demonstrates eosinophilia (often >10%).
- *CXR:* often shows pulmonary opacities (although ~25% have a normal CXR). CT chest can be used to better delineate chest findings.
- *ECG:* generally non-specific findings, including TWI, may suggest eosinophilic myocarditis.

Cardiovascular involvement

- Associated with ↑ peripheral eosinophilia at diagnosis and is an adverse prognostic feature.
- *Eosinophilic myocarditis:* may be suggested by ECG abnormalities, cardiac MRI, and ↑ biomarkers. It may be complicated by HF or mural thrombus (see ➲ Hypereosinophilic syndrome, p. 264 for myocardial disease).
- *Pericarditis:* affects 15–20% and can result in cardiac tamponade.
- *Other cardiac findings*: endomyocarditis, AR/MR, ventricular dysfunction, and arrhythmias/conduction deficits. Coronary arteritis/spasm is seen in a minority of patient.

Treatment

- *Corticosteroids*: these are the mainstay of initial treatment.
- *Cyclophosphamide:* used in severe or life-threatening complications.

Granulomatosis with polyangiitis

- Previously known as Wegener's granulomatosis.

Epidemiology

- Rare condition, with an estimated UK incidence of ~1/100,000 per year.
- Predominantly occurs in people of northern European ancestry and is more common in men than in women (1.5:1).
- Most commonly occurs at age 35–55 years.

Clinical features

- Characterized by upper/lower respiratory tract disease.
- *Ear, nose, and throat (ENT):* subglottic stenosis, chronic nasal crusting, sinusitis, otitis media, and hearing loss.

- *Respiratory:* lung infiltrates, cavitating pulmonary nodules, and pulmonary haemorrhage.
- *Renal disease:* ranges from asymptomatic nephritic sediment to rapidly progressive glomerulonephritis.

Investigations

- *ANCA:* positive in almost all those with active granulomatosis with polyangiitis (GPA), typically PR3.
- *CXR:* often shows multiple, generally diffuse nodules or masses.
- *Pulmonary function testing:* should be used to obtain a baseline and identify abnormalities—may be either restrictive or obstructive.
- *Biopsy:* for histological diagnosis. Often obtained by bronchoscopy.

Cardiovascular involvement

- Less frequent than in eosinophilic granulomatosis with polyangiitis (EGPA), occurring in ~3% of cases.
- *Pericarditis:* most common cardiac complication (~1% of cases).
- *Other infrequent findings:* cardiomyopathy, CAD, and VHD (all <1% of cases).

Treatment

- Treatment recommendations depend on the severity of disease and generally involve corticosteroids and cyclophosphamide/rituximab.

Microscopic polyangiitis

Epidemiology

- Estimated UK incidence of ~2 cases per 100,000 persons/year.
- More common in those of white ethnicity and in men vs women.

Clinical features

- Generally similar findings to GPA, but lack granulomatous ENT and respiratory features and presents with more systemic features.
- Pulmonary–renal syndrome with necrotizing glomerulonephritis and pulmonary haemorrhage is more prominent.

Investigations

- *ANCA:* positive in ~80%; MPO more common than PR3 (60% vs 40%).
- *CXR:* bilateral nodular/patchy opacities or diffuse infiltrates.
- *Renal function:* features of renal dysfunction are common. Urine dip may show proteinuria and/or haematuria.
- *Biopsy:* may be required for histological diagnosis.

Cardiovascular involvement

- Cardiac involvement is generally similar to that of GPA.

Treatment

- *Remission:* principally achieved through use of corticosteroids and either cyclophosphamide or rituximab.
- *Remission maintenance:* generally by using methotrexate or azathioprine ± corticosteroid therapy.

Vasculitides: polyarteritis nodosa

- An ANCA-negative vasculitis of medium-sized arteries.

Epidemiology

- A rare condition, with an estimated incidence of 3–4/100,000 per year.
- More common in women than in men (~2:1), with most common age of onset of 45–65 years.
- Most cases are idiopathic. Previously hepatitis B infection was seen in 30–50% of cases; however, widespread vaccination has reduced this to <10% of polyarteritis nodosa (PAN) cases.
- Hepatitis C and hairy cell leukaemia are also implicated in a subset of cases.

Clinical features

- Spectrum of severity, ranging from single-organ disease through to multiorgan compromise.
- Classically characterized by constitutional upset (e.g. fever, malaise, fatigue), combined with musculoskeletal symptoms (myalgia, large joint arthralgia).
- *Mesenteric arteritis:* abdominal pain, intestinal angina, haemorrhage.
- *Renal artery involvement:* hypertension, flank pain.
- *Central nervous system:* typically transient monocular blindness; less commonly encephalopathy or seizures.
- *Peripheral nervous system:* asymmetric distal neuropathy, mononeuritis multiplex.
- *Skin:* ulcers, nodules, livedo reticularis.

Investigations

- *Blood tests:* findings are generally non-specific. ESR/CRP ↑. FBC shows leucocytosis and normocytic anaemia. ↑ ALT/AST.
- *Hepatitis:* hepatitis B surface antigen and hepatitis C antibodies should be assessed for in all suspected cases of PAN.
- *Angiography:* may demonstrate aneurysms/stenoses in medium-sized vessels. Traditional angiography is more sensitive in detecting small aneurysms; however, CT/MR angiography is commonly used.
- *Biopsy:* obtained from accessible tissue (e.g. skin, skeletal muscle) for histological assessment. Renal biopsies should be avoided due to risk of aneurysmal rupture.

Cardiovascular involvement

- Cardiac disease affects ~35% of those with PAN.
- *Coronary arteritis:* is recognized in PAN, leading to angina or ischaemic cardiomyopathy.
- *Refractory hypertension:* secondary to renal involvement—may also precipitate HF.

Coronavirus disease 2019

- Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- This virus resulted in a pandemic starting in early 2020.
- SARS-CoV-2 can infect the heart and other tissues through angiotensin-converting enzyme 2 (ACE2).

Epidemiology

- COVID-19 developed following a number of similar conditions resulting from related coronaviruses in the early twenty-first century (severe acute respiratory syndrome in 2002 and Middle East respiratory syndrome in 2012).
- By September 2021, SARS-CoV-2 had infected >200 million people, resulting in >4.5 million deaths.

Clinical features

- COVID-19 typically presents with fever and cough. However, a substantial proportion are asymptomatically infected.
- The majority of cases are mild, but a minority will require admission necessitating supplemental oxygenation or respiratory support.

Investigations

- *Blood results:* will often demonstrate raised inflammatory markers with lymphopenia. D-dimer is often raised.
- *Reverse transcription PCR:* used to detect SARS-CoV-2 viral RNA.
- *CXR:* often demonstrates ground-glass opacity but may be normal.
- *Chest CT:* may be considered in those who are seriously ill if the CXR is uncertain or normal.
- *Troponin:* may be raised in severe disease and does not necessarily represent an acute cardiac event.

Cardiovascular involvement

- *HF:* this is common in severe COVID-19 (3–33%), with a subpopulation developing cardiogenic shock. May be due to myocarditis in some cases.
- *Arrhythmias:* supraventricular and ventricular arrhythmias may be seen in a minority of patients (9–17%).
- *VTE:* DVT/PE is common in those with COVID-19 (~25%) and there should be a low threshold for investigating for this outcome.
- Rarely, a KD-like paediatric multisystem inflammatory syndrome has been observed associated with COVID-19, with typical fever, rash, mucositis, and conjunctivitis.

Treatment

- The majority of patients do not require admission and can be managed with supportive therapy.
- *Oxygen therapy:* should be given in those with low oxygen saturations or other features that suggest respiratory distress.
- *Ventilatory support:* considered for a subset of patients when supplemental oxygen is insufficient.
- *Corticosteroids:* in patients requiring oxygen, corticosteroid therapy (dexamethasone 6mg daily for 7–10 days) should be considered.
- *Casirivimab and imdevimab:* these are monoclonal antibodies against the SARS-CoV-2 spike protein. They should be given in combination to those hospitalized with COVID-19 without SARS-CoV-2 antibodies.
- *Tocilizumab:* should be considered in those who have completed corticosteroids and still require oxygen therapy and have a CRP level ≥75mg/L.
- *LMWH:* standard prophylactic doses should be given to all patients admitted with COVID-19 who do not have contraindications. This should be continued until discharge or for a minimum of 7 days (whichever is longer).
- *CV management:* most patients do not require CV management. However, patients with HF or arrhythmias should be investigated and treated as for those without COVID-19.

Connective tissue disorders: Marfan syndrome

- A spectrum of presentations related to a mutation in the *FBN1* gene principally affecting connective tissues. Over 1500 described mutations in the *FBN1* gene encoding fibrillin-1 on chromosome 15q21.1.
- Fibrillin-1 glycoprotein is an integral component of microfibrils in connective tissues. In Marfan syndrome, the structural integrity of vascular, ocular, and skeletal connective tissue is compromised.

Epidemiology

- Autosomal dominant disorder with a spectrum of clinical severity.
- Incidence is 1/5000 worldwide.

Clinical features

- Phenotype varies widely.
- Aortic root disease and ectopia lentis (80%) are the two major features.
- Other features include arachnodactyly, long limbs, scoliosis, pectus excavatum and carinatum, joint hypermobility, chest wall deformities, spontaneous pneumothorax or spinal arachnoid cysts, ocular defects, skin striae, and recurrent herniae.

Features of Marfan syndrome

- *Wrist sign:* the thumb and fifth finger overlap each other when wrapped around the other wrist.
- *Thumb sign:* the adducted thumb protrudes beyond the ulnar border of a clenched fist.
- *Facial features:* dolichocephaly (premature closure of the sagittal skull suture, resulting in impaired lateral growth), malar hypoplasia, enophthalmos, retrognathia, and down-slanting palpebral fissures.

Cardiac involvement

Aortic disease

- Aneurysmal aortic root dilatation, AR, and dissection are the leading cause of morbidity and mortality.
- Root disease involves the sinus of Valsalva. Evident in childhood in ~50%. Progresses with age. Poorly correlated with other features.
- The thoracic aorta may also be involved.

Valvular heart disease

- MVP affects 40–50%.
- Mild MR is common; progression and associated HF develop in ~25%. Spontaneous chordae tendinae rupture can occur.

Investigations

- *Cardiac imaging:* echocardiography/MRI/cardiac CT assessing the MV and aortic valve, aortic root, and ascending aorta. Aortic root dilatation should be indexed to height.

- *Slit-lamp examination and ophthalmology assessment:* warranted to identify retinal detachment, lens dislocation, progression of cataract, myopia, or open-angle glaucoma.
- *Genetic testing:* limited role in diagnosis. First-degree relatives may be offered genetic counselling ± testing to guide aortic surveillance.

Treatment

- *Prophylaxis:* β-blockers and ARBs (e.g. losartan) reduce progression of aortic dilatation or rate of complications.
- *Aortic surgery:* recommended if maximal aortic diameter ≥50mm. A lower threshold (e.g. 45mm) is considered if additional risk factors, severe AR, family history of dissection, or size ↑ by >3mm per year, or in pre-pregnancy planning.
- *Light exercise and physiotherapy:* can help associated musculoskeletal biomechanical pain and injury.

Revised Ghent criteria for Marfan syndrome

For the full Ghent criteria for Marfan syndrome, see: 🖱 https://jmg.bmj.com/content/47/7/476

Connective tissue disorders: Ehlers–Danlos syndrome

- Inherited disorder leading to altered synthesis and metabolism of different types of collagen, resulting in structural defects in the skin, skeleton, ligaments and tendons, vasculature, and eyes.
- Rarer forms associated with genetic mutations affecting other extracellular matrix components such as glycosaminoglycans (see Table 10.2).

Epidemiology

- Autosomal dominant and recessive inheritance.
- One in 5000 live births, with no geographical or ethnic predisposition.
- Typically presents between childhood and early adulthood.
- Thirteen subtypes recognized by international classification, including classical, hypermobile, kyphoscoliotic, and vascular EDS.

Clinical features

- Joint hypermobility (see Box 10.2), skin hyperextensibility, tissue fragility, and poor wound healing feature in varying degrees in several forms of EDS.
- Joint hypermobility predisposes to biomechanical pain and accelerated osteoarthritis.
- Classic EDS is associated with ‘doughy’, hyperextensible skin, with ‘cigarette paper’ scarring over the knees. Hernias are common.

Cardiovascular involvement

CV features are principally seen in cardiac–valvular and vascular forms of EDS.

- *MVP:* seen in several subtypes, but only progresses to significant MR in a minority.
- *Aortic root dilatation:* affects ~12% in hypermobile EDS. Rarely severe or progressive, and aortic root replacement is exceptional.
- *Autonomic instability:* may be evident, particularly in hypermobile EDS, and can include postural orthostatic tachycardia syndrome (POTS).

Box 10.2 Beighton score

Screening technique for hypermobility. Nine-point scale requiring performance of five manoeuvres (four bilateral and one spinal). Score of 0–3 is normal; 4–9 suggests ligamentous laxity. Joints involved in the score:

- Passive dorsiflexion and hyperextension of the fifth metacarpophalangeal joint >90°
- Passive apposition of the thumb to the flexor aspect of the forearm
- Passive hyperextension of the elbow >10°
- Passive hyperextension of the knee >10°
- Active forward flexion of the trunk, so that the palms of the hand rest flat on the floor, with the knees fully extended.

Source: data from Beighton P *et al*. Orthopaedic aspects of the Ehlers–Danlos syndrome. *J Bone Joint Surg Br* 1969;**51**(3):444–53.

- *Vascular EDS*: life-threatening due to spontaneous vascular or visceral rupture, whereas joint and skin manifestations are typically minimal. Life expectancy is significantly reduced. Major vascular events are typically unheralded and occur under the age of 50 years.

Treatment

- There is no specific medical therapy.
- Patient education, preventive strategies, and pain management are important.
- Regular eye and dental assessments.
- Complex EDS is managed by specialist centres. Genetic counselling may be offered. There is a limited role for genetic testing.

Table 10.2 Selected EDS types

Type	Former name	Genetic mutations	Clinical features
Classical	EDS I/II	*COL5A1*, *COL5A2*	Classic features
Classical-like	–	*TNXB*	Classic features with easily bruised skin
Cardiac–valvular	–	*COL1A2*	Severe aortic valve and mitral valve disease
Vascular	EDS IV	*COL3A1*	Life-threatening haemorrhage
Kyphoscoliotic	EDS VI	*PLOD1*, *FKBP14*	Scoliosis and significant eye problems
Arthrochalasia	EDS VII	*COL1A1*, *COL1A2*	Joint hyperlaxity with congenital dislocations
Hypermobile	EDS III	None identified	Marked joint laxity

Source: data from Malfait *et al*. The 2017 international classification of the Ehlers–Danlos syndromes. *Am J Med Genet*. 2017;**175C**:8–26.

Rheumatic drug therapy and the heart

Rheumatic drug therapies commonly used in rheumatic disease or with specific relevance to the CV system are considered here.

Non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors

- Both non-selective NSAIDs and COX-2-selective NSAIDs (-coxibs) are associated with ↑ risk of CV events.
- Naproxen or low-dose ibuprofen (1200mg/ daily) are considered to have the most favourable CV safety profile.
- *HF*: associated with a 10-fold risk of symptomatic HF in patients with a history of cardiac disease (and doubling of risk in those without).

Anti-TNF-α therapies (adalimumab, etanercept, infliximab)

- Approved for treatment of RA, AS, and psoriatic arthritis, as well as inflammatory bowel disease, uveitis, and psoriasis.
- *Cardiac contraindications/cautions:* clinical trial and post-marketing surveillance suggest treatment may be associated with exacerbation of, or new-onset, HF. Treatment is therefore contraindicated in patients with NYHA class III or IV HF. Caution should be used in milder HF.
- *Cardiac adverse effects:* arrhythmias, chest pain, and hyper-/hypotension are common adverse effects of infliximab and adalimumab. Etanercept has no common cardiac adverse effects documented.
- *Discontinuation:* anti-TNF-α treatment should be stopped in patients with new-onset HF, and patients evaluated carefully for the underlying aetiology.
- *Cardiac drug interactions:* no substantial cardiac drug interactions for TNF-α inhibitors.

Anti-interleukin-6 receptor biologics (tocilizumab, sarilumab)

- Approved for treatment of RA, GCA, juvenile arthritis, and adult-onset Still's disease.
- *Cardiac contraindications/cautions:* no cardiac contraindications or cautions.
- *Cardiac adverse effects:* tocilizumab and sarilumab cause early ↑ serum lipids, which usually stabilizes within 4 months. Associated ↑ in cardiac events has not been found, suggesting suppression of inflammatory disease offsets the atherogenic effect. However, introduction of lipid-lowering therapy should be considered, based on the individual's overall CV risk.
- *Monitoring:* should monitor lipid profile 4–8 weeks after initiation and then 6-monthly.
- *Cardiac drug interactions:* tocilizumab ↑ exposure of CCBs, statins, and warfarin. Sarilumab reported to ↑ exposure of statins and warfarin.

Oral Janus kinase (JAK) inhibitors (baricitinib)

- Approved for treatment of RA and moderate to severe atopic eczema.
- *Cardiac contraindications/cautions:* no cardiac contraindications or cautions reported.

- *Cardiac adverse effects:* blocks intracellular signal cascades downstream of IL-6—may provoke similar rises in serum lipids and warrant similar monitoring. ↑ risk of VTE.
- *Cardiac drug interactions:* no substantial cardiac drug interactions have been reported.

Anti-CD20 biologic agents (rituximab)

- Licensed for use in RA. Used in GPA and microscopic polyangiitis (MPA).
- *Cardiac contraindications/cautions:* contraindicated in severe HF or uncontrolled heart disease. Caution in patients with a history of CVD due to risk of adverse effects. Caution in patients undergoing cardiotoxic chemotherapy.
- *Cardiac adverse effects:* MI, arrhythmias, chest pain, and hyper-/hypotension are recognized adverse effects.
- *Cardiac drug interactions:* no substantial cardiac drug interactions have been reported.

Interleukin-1 receptor antagonist (anakinra, canakinumab)

- Licensed for RA, Still's disease, and gout (canakinumab only).
- *Cardiac contraindications/cautions:* no cardiac contraindications or cautions.
- *Cardiac adverse effects:* no common CV adverse effects reported.

Bisphosphonates (zoledronic acid, pamidronate, alendronic acid)

- Used as for primary and secondary prevention of osteoporotic fractures, treatment of Paget's disease, and as adjuncts to some cancer treatment.
- Clinical trial data suggest a possible small ↑ risk of AF associated with zoledronic acid and pamidronate treatment, and possibly with PO alendronic acid.

Erectile dysfunction

Definition

Erectile dysfunction (ED) is inability to achieve or maintain a penile erection that is sufficient for satisfactory penetrative sexual intercourse.

Epidemiology

- Currently 150 million men worldwide have ED.
- Prevalence ↑ with age: 40% of men aged over 40 years and 70% aged over 70 years are affected.

Causes

- Atherosclerotic vascular causes are the most common.
- Prevalence of ED in diabetes >70%, and in hypertension >60%.
- Coexisting CAD is found in 50–75%.
- Metabolic syndrome, obesity, physical inactivity, hyperlipidaemia, smoking, and alcohol excess are significant risk factors.
- *Other pathological causes:* psychological factors (usually younger men with premature ejaculation), neurological (multiple sclerosis, Parkinson's disease, radical non-nerve-sparing prostatectomy), endocrine (diabetes, hypogonadism).
- *Causative drugs:* include antihypertensives, antidepressants, antipsychotics, and recreational drugs such as cannabis and cocaine.

Investigations

- ED is a marker for asymptomatic CVD and manifests 2–5 years before a cardiac event; therefore, CV risk assessment and a primary prevention approach are warranted.
- Thyroid function, testosterone (free), and sex hormone-binding globulin (SHBG) before 11 a.m. should be considered.

Treatment (general)

- Sensitive counselling and lifestyle advice (smoking, exercise).
- *Phosphodiesterase type 5 (PDE-5) inhibitors:* such as sildenafil and tadalafil—can be initiated in primary care and are highly efficacious.
- *Second-line interventions:* generally under specialist supervision; include prostaglandins by intracavernosal injection, vacuum devices, and penile implants.
- *Testosterone replacement:* may be warranted and appropriate replacement improves libido, CV risk status, and efficacy of PDE-5 inhibitors.

Chronic kidney disease

- CKD is defined as an estimated GFR (eGFR) of <60mL/min/1.73m² for ≥3 months, irrespective of the cause.
- In patients with CAD, concomitant CKD heralds a worse prognosis.
- CV morbidity and mortality are inversely and independently associated with kidney function, particularly when eGFR is <15mL/min/1.73m² (end-stage renal failure (ESRF)).
- Renal function should be assessed in those with cardiac pathology.

A cardiac cause is implicated in >40% of all deaths at ESRF.

Assessment of renal function

- Based primarily on two parameters—the GFR and *urinary albumin* (in more advanced stages of CKD, there is unselective proteinuria).
- In early CKD, ↓ GFR is still compatible with normal serum creatinine concentrations as serum creatinine also depends on non-renal factors, particularly muscle mass.
- More accurate estimates of GFR (eGFR) are possible by measurement of serum creatinine with validated methodology (MDRD (Modification of Diet in Renal Disease), CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)) and by correcting for age, sex, and ethnicity.
- GFR not validated in pregnancy (serum creatinine values used).

Urinary excretion of albumin

- ↑ urinary excretion of albumin is the earliest manifestation of CKD due to diabetes and hypertensive nephrosclerosis, and is a powerful predictor of risk and progression of CVD.
- This is defined as an albumin:creatinine ratio (ACR) of >30mg/g in two of three spot urine specimens.
- Measurement of 'spot' ACR is inaccurate in the context of acute kidney injury (AKI), and a 24h urine collection should be performed to accurately quantify this.

Cardiovascular risk in chronic kidney disease

- Both GFR and albuminuria independently contribute to CV risk.
- In the absence of albuminuria, the CV risk conferred by ↓ renal function is markedly less.
- ↓ renal function impacts CV risk not only in patients with primary kidney disease; ↓ renal function is also a major risk factor for cardiac events in primary cardiac disease, particularly CAD and HF.

Hypertension in chronic kidney disease

- ↑ BP is a major cause of CV risk in CKD. Most patients will require ≥2 antihypertensive agents.
- Renal patients, particularly diabetic patients with nephropathy, are characterized by nocturnal non-dipping and ↑ BP amplitude.
- Ambulatory BP measurements and home BP monitoring are a valuable tool.
- Target BP of 140/90mmHg if not proteinuric.

- Target of 130/80mmHg if proteinuric or diabetic.
- RAAS blockade further ↓ proteinuria, in part independently of BP.

Mechanisms by which renal impairment affects cardiac function

- ↑ blood pressure
- ↑ sympathetic activity and ↓ catecholamine breakdown (renalase)
- Lipid abnormalities (e.g. Lp(a), small and dense low-density lipoprotein, remnants, modified apolipoproteins
- ↑ oxidative stress and microinflammation
- ↑ serum phosphate and the phosphaturic hormone fibroblast growth factor 23
- ↑ asymmetric dimethylarginine

Cardiac death in chronic kidney disease

Cardiac arrest

- The most frequent cause of death in those with CKD, followed by HF and death from other cardiac causes (e.g. aortic valvular disease).
- SCD accounts for ~25% of dialysis patient deaths, with an annual rate of 5.5% and those surviving have a 6-month survival of 3–11%.
- Secondary analyses of patients with moderate CKD enrolled in the MADIT-II and COMPANION trials have found an ↑ risk of SCD with ↓ baseline GFR (commonest after a 2-day dialysis break).
- Therapeutic interventions are limited: β-blockers have been proven to be useful in CKD patients with DCM, but the wider scope of their utility has not been determined.
- ICDs may be helpful. Observational data suggest modestly improved survival of dialysis cardiac arrest survivors receiving ICDs for secondary prevention, whereas USRDS reports median survival of only 18 months in those receiving an ICD for primary prevention.

Acute coronary syndrome

- ↑ compared with background population, but accounts only for ~9% of deaths.
- In CKD, particularly in uraemia, patients develop biventricular hypertrophy, cardiac fibrosis, and microvascular disease, with ↓ coronary reserve, ↓ capillary density, and ↓ ischaemia tolerance. In dialysed patients, stunning is frequently observed during dialysis.
- Diagnosis of ACS is difficult in CKD, as ischaemic symptoms and ECG changes are frequently absent and cardiac biomarkers may be deranged in CKD patients. LVH with a strain pattern may mask diagnostic ST-segment depression.
- Presentations with systolic or diastolic dysfunction causing HF symptoms or with syncope are more common.
- CK-MB and troponin may be ↑ in the absence of MI. Trends over time are likely more useful than single test values.

CKD: investigations

Renal investigations in a patient with cardiac disease

- *All patients:* assess race-corrected MDRD or CKD-EPI eGFR and albuminuria or proteinuria, respectively. Need steady-state creatinine; inaccurate at extremes of weight, pregnancy, or age <18 years.
- *If primary kidney disease suspected:* urine dipstick, bloods for vasculitides, serum free light chains and serum protein electrophoresis for myeloma, hepatitis B and C/HIV, PLA2R if nephrotic-range proteinuria (>3g/24h), and renal US.
- *If renovascular disease suspected:* use duplex sonography or MRA.

Cardiac investigations in a patient with renal disease

- *Consider in all patients:* ECG and echocardiographic evaluation to detect inappropriate LVH, LV dysfunction, and, in advanced stages, pericardial effusion.
- *In those with ESRF*: metabolic skeletal myopathy usually precludes meaningful evaluation by treadmill testing. Pharmacological stress testing permits non-invasive ischaemia detection (particularly relevant if renal transplantation is considered). CMR is helpful, but gadolinium should be used with caution in advanced CKD (see ➔ Gadolinium-based contrast agents, pp. 464–5).
- *Coronary angiography:* remains the gold standard for diagnosis of CAD. It is often underused due to concerns about radiocontrast nephropathy (see ➔ Iodine-based contrast agents, p. 464), but should definitely not be withheld in patients with ACS.

Adverse effects of cardiac investigations in those with chronic kidney disease

Iodine-based contrast agents

- AKI following contrast administration is associated with death, hospitalization, and future CV events.
- Risk factors include CKD, DM, HF, ↑ age, volume depletion, and ↑ BP.
- The effects are more marked with arterial over venous contrast.
- Strategies to reduce the incidence include:
    - Cessation of nephrotoxic agents—ACEis/ARBs, metformin; avoidance of other nephrotoxics (e.g. NSAIDs, aminoglycosides) and diuretics 24h before and 48h post-administration
    - Contrast agent selection: use of iso-osmolar, non-ionic contrast; <100mL contrast volume if possible
    - Volume status: optimization pre-study
    - No benefit of IV $NaHCO_3$ vs IV NaCl or PO acetylcysteine vs placebo on death/dialysis/AKI in CKD stages 3–4 (PRESERVE trial).

Gadolinium-based contrast agents

- MRI, using gadolinium-based contrast agents (GBCAs) should be avoided, where possible, when eGFR is <30mL/min/1.73m^2, with rising creatinine leel, or in cases of AKI.
- Risk of acute reactions and chronic toxicity (i.e. nephrogenic systemic fibrosis (NSF)). NSF is extremely rare, but potentially life-threatening, and may present acutely or many years later.

- If necessary, the single lowest-risk agent should be used (<0.1mmol/kg) and should not be repeated within 7 days.
- Patients established on dialysis should be dialysed promptly (within 24h) following contrast. There is no evidence to support dialysis initiation for CKD patients not already on dialysis.

CKD: prevention and treatment of cardiovascular sequelae in renal patients

Limited evidence available, but current strategies include the following.

Blood pressure control

- The most important component of treatment (see ➔ Cardiovascular risk in chronic kidney disease, p. 462).
- Specific targets vary between NICE, KDIGO (Kidney Disease Improving Global Outcomes), and UK Kidney Association but should generally aim for <130/80mmHg in CKD patients.
- Antihypertensives ↑ the risk of hypotensive episodes during ultrafiltration. Advise patients to take *after* dialysis session on dialysis days.

Reduction of salt intake

- Essential for diuretic efficacy, more effective than fluid restriction.
- ↓ BP and ↓ proteinuria. Effects on CVD not well established.
- Aim for intake of <100mmol/day (5–6g); typical UK intake 9–12g.
- Should avoid salt substitutes (e.g. *Losalt)* as they contain potassium chloride (KCl).

Blockade of the renin–angiotensin–aldosterone system

- Inappropriate activation of the RAAS is a hallmark of CKD.
- RAAS blockade confers benefit beyond ↓ BP and mitigates ↓ renal function at least in proteinuric patients.
- Less than 25% change in GFR following initiation is acceptable to continue.
- Initiation of ACEi/ARB should be cautious in CKD stage 5 due to risk of ↑ K^+ level or ↓ GFR necessitating dialysis.
- Unclear whether stopping ACEis/ARBs in CKD stage 5 may delay dialysis.
- ACEi/ARB dose should be optimized before the addition of additional agents.

Sodium-glucose co-transporter-2 inhibitors (SGLT2i)

- Significant effect in slowing rate of kidney function decline and modifying cardiovascular risk.
- Dapagliflozin reduces all-cause mortality by 30% in those with CKD and 37% reduction in significant renal/cardiovascular mortality.
- Currently contraindicated in polycystic kidney disease, T1DM, and in those with kidney transplants.
- The UK Kidney Association recommends SGLT2i initiation in those with CKD $^{+}/^{-}$ T2DM when the eGFR 20–45 ml/min/1.73m^2, eGFR >45ml/min/1.73m^2 and ACR ≥25mg/mol, symptomatic heart failure, or established coronary disease.

Potassium lowering therapy

- Sodium zirconium cyclosilicate and patiromer are licensed oral K^+ binding agents and may be used in AKI/CKD to manage ↑ K^+.
- Sodium zirconium cyclosilicate is recommend for treating hyperkalaemia in adults when: in an emergency setting for acute life-threatening hyperkalaemia, in those with persistent hyperkalaemia with CKD (stage 3b to 5) or heart failure, or where optimization of RAAS inhibition is limited by hyperkalaemia.

β-blockers

- ↑ sympathetic activity in CKD. Thus, rational to give β-blockers, specifically those without metabolic effects (carvedilol, nebivolol).
- β-blockers can be considered in those with CKD and hypertension and may be effective for ↓ sudden cardiac death.

Mineralocorticoid receptor blockers

- Spironolactone ↓ proteinuria in patients if proteinuria not adequately ↓ by RAAS blockade or ↑ after an initial ↓ (so-called 'escape').
- Fourth-line antihypertensive agent in CKD patients (NB despite fewer side effects, eplerenone is not licensed for this indication).
- Must monitor for ↑ K^+, and give dietary advice on ↑ K^+-containing foods (e.g. tomatoes, spinach, melons, bananas, nuts, dried fruit, avocados).
- Finerenone is a non-steroidal mineralocorticoid receptor antagonist indicated in CKD stage 3 and 4 with albuminuria. Dosing is dependent on eGFR and serum K^+ level.

Diuretics

- Loop diuretics should be continued in CKD stages 4–5 as part of fluid management if urine output is >200mL/24h for prognostic benefit.
- Note ↑ doses will be required as tubular secretion ↓ in end-stage kidney disease, and care should be taken regarding ototoxic effects.
- Metolazone is a useful adjunct as a thiazide-like diuretic, in combination with a loop diuretic, to potentiate diuresis.
- Continuous furosemide infusion ↑ diuresis vs bolus, but no difference in time to discharge, renal impairment, or electrolyte disturbance.

Alkalinizing agents

- Correction of acidosis with sodium bicarbonate confers a survival benefit for CKD patients; aim for bicarbonate level of >23mmol/L.
- This is also a useful adjunct in managing hyperkalaemia.
- Will ↑ fluid retention, so may require compensatory ↑ diuretic.

Anaemia

- Anaemia becomes more prevalent as eGFR falls and has a significant effect on CV outcomes, particularly in HF.
- Hb levels should be targeted at 100–120g/L.
- Supplement iron if ferritin <100mcg/L or transferrin saturation is <20%.
- Usually given as IV iron, but PO iron may be trialled in CKD stages 1–3.
- Patients may also be on erythropoietin (IV on dialysis or s/c) or hypoxia inducible factor (HIF) stabilizers prescribed by the renal team.
- Do not overtreat anaemia as trials demonstrate ↑ incidence of MI and stroke if Hb concentration is restored to 'normal levels' (>120g/L).
- Avoid red cell transfusion, wherever possible, to limit sensitization, which affects transplantation options.

Statins

- Evidence of benefit for lipid-lowering therapy in CKD is limited.
- The SHARP study suggested a benefit of simvastatin for major atherosclerotic events in those with CKD stages 3–5. The 4D and AURORA studies showed no benefit of statins in dialysis-dependent patients.

- Current ESC guidelines define all patients with eGFR ≤60mL/min/1.73m^2 to be at high or very high CV risk.
- Given conflicting trial results, statins should be initiated in those with CKD stages 3–5 (Class IA), but not in those without CVD who are dialysis-dependent (Class IIIA).
- Those on statins when they start dialysis should continue.
- Statin side effects are ↑ with CKD, especially myopathy, so use ↑ doses with caution. Interaction between ciclosporin and statins.
- Ezetimibe is considered safe, with no dose modification.

Mineral bone disease

- CKD stage 3–5 patients with known vascular or valvular calcification are considered at highest CV risk.
- Treatment based on serial assessments of phosphate (PO_4^{2-}), Ca^{2+}, and PTH.
- Persistently/progressively ↑ PO_4^{2-} should be ↓ to normal range by limiting dietary intake (eggs, dairy) and using non-Ca^{2+}-containing binders if also ↑ Ca^{2+} (e.g. sevelamer), or if ↓ Ca^{2+}, calcium carbonate.
- ↑ Ca^{2+} should be avoided, as recent studies have associated ↑ concentrations of serum Ca^{2+} with non-fatal CV events.
- In CKD stages 3–5, calcitriol and vitamin D analogues should not be routinely used (KDIGO Class IIc). Should be used in CKD stages 4–5 with severe and progressive hyperparathyroidism (Class IIb).

Chapter 11

Cardio-oncology

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Common cardiovascular effects 472
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General principles of management and prevention of cardiotoxic effects 478
Follow-up of early and late effects of cancer therapy 480

What is cardio-oncology?

- The subspecialty of cardio-oncology is a relatively new and rapidly expanding field, which facilitates prevention, early diagnosis, treatment, and follow-up of CV complications arising from the use of cancer therapies.
- Advances in such therapies have ↑ dramatically over the last few decades, leading to ↑ survival (see Fig. 11.1), however, at the cost of a concomitant ↑ in CV mortality and morbidity.
- CV complications occur as a direct result of cardiotoxicity or may be due to CVD, the development of which may be accelerated in individuals with underlying risk factors.
- As a developing field, there is still much to learn regarding the long-term CV effects of both radiation and chemotherapy.
- This lack of knowledge may lead to inappropriate cessation of potentially lifesaving therapies, as well as failure to prevent CV complications.
- Cardio-oncological units should comprise not only oncologists and cardiologists, but also a wider MDT (including haematologists, specialist nurses, physiologists, and physiotherapists), able to make decisions around acute care, as well as longer-term surveillance strategies.

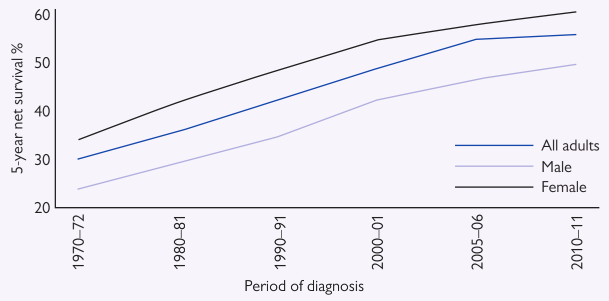

Fig. 11.1 Survival of all cancers in England (1971–2018).

This material has been reproduced from the World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: A Global Perspective*. Continuous Update Project Expert Report 2018. Available at ☞ dietandcancerreport.org.

Common chemotherapeutic agents

Chemotherapeutic agents can be divided into cytotoxic agents and molecular targeted therapies. Table 11.1 demonstrates the mechanisms of action and targets of commonly used agents.

Table 11.1 Commonly used chemotherapeutic agents and their mechanisms of action

Agent type	Example	Mechanism of action	Cancer target
Cytotoxic agents	Anthracyclines (e.g. doxorubicin)	Inhibits topoisomerase II, causing accumulation of double-stranded DNA breaks, dysfunction of mitochondria, and activation of cell death pathways. Accumulation of reactive oxygen species also damages cells	Leukaemia Soft tissue
	Taxanes (e.g. docetaxel, paclitaxel)	Disrupt microtubules, thereby disrupting cell division	Breast Ovarian
	Others (e.g. fluorouracil, cisplatin, cyclophosphamide)	Binds to DNA, causing cross-linking and apoptosis	Ovarian Bladder Testicular
Molecular targeted therapies	Human epidermal growth factor receptor 2 (HER2) antibody (e.g. trastuzumab)	Monoclonal antibody directed against HER2 protein	Breast
	Tyrosine kinase inhibitors (e.g. imatinib, sunitinib)	Blocks signal transduction responsible for protein activation	Breast Gastrointestinal Renal Leukaemia Non-Hodgkin's lymphoma
	Vascular endothelial growth factor (VEGF) inhibitors (e.g. sorafenib)	Inhibits angiogenesis mediated by VEGF and VEGF receptors	Brain Lung Kidney Colon cancer
	Other agents (e.g. rituximab)	Monoclonal antibody directed against CD20 protein	Leukaemia Lymphoma

Source: data from Ghosh AK *et al*. *British Journal of Hospital Medicine* 2017 **78**:C11–C13.

Common cardiovascular effects

- The concept of cardiotoxicity has been recognized for ≥50 years.
- Complications can be divided into subcategories. See Table 11.2 for CV effects of common cancer therapies.
- These complications may arise acutely; however, some complications may occur after a number of years.

Cardiovascular effects of common cancer therapies

Anthracyclines

- Anthracyclines commonly cause LV dysfunction. This may occur acutely in <1% of individuals and is usually transient. Early effects occur in the first year of treatment, whereas late effects occur several years following treatment.
- Non-specific ECG changes/↑ QTc can occur during infusion.
- Those with established cardiomyopathy may experience NSVT (~75%) and AF (~50%) or more malignant arrhythmias. May be aggravated by ↑ K^+. Arrhythmias appear to be dose-independent.

Human epidermal growth factor receptor 2 inhibitors

- Human epidermal growth factor receptor 2 (HER2) inhibitors may also ↑ the incidence of HF.
- LV dysfunction secondary to HER2 inhibitors generally manifests at the time of therapy and is usually reversible.
- Cardiotoxicity risk may be reduced by using an anthracycline-free regime or by sequential (cf. concomitant) use following anthracyclines.

Vascular endothelial growth factor inhibitors

- Vascular endothelial growth factor (VEGF) inhibitors may cause LV dysfunction, including Takotsubo cardiomyopathy. They may often give rise to hypertension.
- Changes in endothelial function and promotion of a prothrombotic state ↑ the risk of angina, ACS, thromboembolic disease, and CVA.
- Arrhythmic risk varies across agents (e.g. sorafenib associated with AF, particularly if combined with fluorouracil (5-FU), vemurafenib associated with ↑ QTc).

Tyrosine kinase inhibitors

- Tyrosine kinase inhibitors (TKIs) may be associated with hypertension, angina, ACS, Takotsubo cardiomyopathy, and thromboembolic disease, as well as CVA.
- Additionally, agents such as nilotinib and ponatinib can cause rapidly progressive atherosclerosis leading to PAD.
- Some TKIs such as dasatinib may cause severe PHT; however, this is usually reversible.
- Ibrutinib is associated with AF in ~5% of cases, usually during the first 4 months. Nilotinib appears to cause the greatest ↑ QTc in this class.

Platinum-based chemotherapy

- Platinum-based chemotherapy (e.g. cisplatin, oxaliplatin) can trigger chest pain secondary to endothelial dysfunction; this, in turn, may lead to altered vasoreactivity and a prothrombotic state.
- These agents can cause hypertension, angina, ACS, CVA, and PAD.
- Platinum-based chemotherapy may lead to volume overload related to the large IV bolus which accompanies administration. This can precipitate HF in those with pre-existing LV dysfunction.
- Systemic use of cisplatin is often associated with sinus bradycardia.
- Cisplatin-induced ↓ Mg^{2+} may cause rhythm disturbance (AF, VT, asystole), even after local use.

Other agents

- 5-FU causes chest pain in up to 20% of individuals due to coronary vasoconstriction and endothelial injury. Supraventricular arrhythmias are uncommon, but VT may be seen in up to 7%. The 5-FU prodrug capecitabine causes chest pain to a lesser degree. 5-FU may also cause LV dysfunction in a number of individuals and may predispose to Takotsubo cardiomyopathy.
- Taxanes can also cause vasoconstriction, leading to angina and ACS, and may additionally cause hypertension. The most common arrhythmia associated with paclitaxel is transient sinus bradycardia, particularly when combined with cisplatin.
- Cyclophosphamide toxicity is rare but may result in LV dysfunction within a few days of administration and can cause PHT. Cyclophosphamide can lead to myocardial ischaemia and angina, and downstream LV impairment. ST-segment and T wave changes, ↑ QTc, and early ↓ in QRS voltage have been reported.
- Immune checkpoint inhibitors are a relatively new class of anti-cancer therapies. These act by ↑ T cell-mediated immune response against cancer cells. Currently licensed checkpoint inhibitors include ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab, which are used in the treatment of metastatic disease, including melanoma, renal cell carcinoma, small cell carcinoma of the lung, and head and neck cancers. These agents have been shown to cause myocarditis. There are limited case reports of AF and malignant ventricular arrhythmias with this new class of drugs.

Radiotherapy

- The effects of radiotherapy (other than the rare acute myocarditis) usually occur after many years.
- Can induce macro- and microvascular damage, leading to fibrosis of the myocardium, as well as CAD by means of endothelial injury, plaque rupture, and thrombosis.
- VHD occurs in around 10% of individuals, and includes fibrosis and calcification of the aortic and mitral valves. This usually spares the mitral valve tips, differentiating this from rheumatic disease.

Table 11.2 Cardiovascular effects of common cancer therapies

Agent	LVSD	HTN	Chest pain	ACS	TCM	CVA	PAD	PHT	DVT/PE	Arrhythmias
Anthracyclines	X									X
HER2 inhibitors	X									X
VEGF inhibitors	X	X	X	X	X	X			X	X
TKIs	X	X	X	X	X	X		X(some)	X	X
Platinum-based		X	X	X		X	X			X
FU	X		X	X	X					X
Taxanes		X	X	X					X	X
Cyclophosphamide	X		X	X				X		

LVSD, left ventricular systolic dysfunction; HTN, hypertension; ACS, acute coronary syndrome; TCM, Takotsubo cardiomyopathy; CVA, cerebrovascular accident; PAD, peripheral arterial disease; PHT, pulmonary hypertension; DVT, deep vein thrombosis; PE, pulmonary embolism; HER2, human epidermal growth factor receptor 2; VEGF, vascular endothelial growth factor; TKI, tyrosine kinase inhibitor; 5-FU, 5-fluorouracil.

Source: data from Chung R, Ghosh AK, Banerjee A. Cardiotoxicity: precision medicine with imprecise definitions *Open Heart* 2018;**5**:e000774. doi:10.1136/openhrt-2018-000774.

Assessment and investigation of the cardio-oncological patient

Risk assessment

- Prediction of the magnitude and timing of complications remains a challenge, as often individuals receive multiple chemotherapeutic agents, as well as radiotherapy, which have the potential to augment cardiotoxic effects. Early identification of potential risk factors is essential in order to guide those individuals who may be more likely to experience adverse effects of therapy.
- Risk factors for developing cardiotoxicity are outlined in Box 11.1.

Investigations

Following a comprehensive history and physical examination, investigations are performed to assess baseline CV function.

ECG

- Enables detection of conduction/rhythm disturbances, ST-segment/T wave changes, and QTc interval (should be <450ms in men and <460ms in women).
- This should be performed at baseline and during therapy.

Cardiac biomarkers

- Cardiac biomarkers, such as troponin and natriuretic peptides (NT-proBNP, BNP), may be useful for serial measurements over time.
- There is insufficient evidence at present to specify the timing of testing and the intervention required with an abnormal result.

Imaging

When choosing an imaging modality, it is important to bear in mind the accuracy and reproducibility of the imaging technique, in order to ensure that changes seen in cardiac structure and function are likely to represent the effects of the therapy.

Box 11.1 Risk factors for developing cardiotoxicity

- Cumulative dose
- Age >65 years or <18 years
- ♀ sex
- Ethnicity (especially Afro-Caribbean)
- Comorbidities (renal failure)
- Existing CVD (LV dysfunction, CAD, hypertensive heart disease, VHD, cardiomyopathy, arrhythmias)
- Existing CV risk factors (♂, diabetes, hypertension, hypercholesterolaemia, family history of CVD <50 years, smoking, obesity)
- Concomitant or previous radiotherapy to chest or mediastinum
- Concomitant or previous chemotherapy (e.g. anthracycline)
- Risk is ↑ in individuals undergoing left-sided irradiation, lack of shielding, higher doses, and concurrent use of other chemotherapeutic agents (e.g. anthracyclines)

Echocardiography

- *Pros:* widely available, inexpensive, enables assessment of cardiac structure and haemodynamics, no radiation.
- *Cons:* interpretation is dependent on image quality and may vary across operators. Should ideally be performed by the same operator on the same machine during follow-up.
- Cancer therapeutics-related cardiac dysfunction is defined as >10% ↓ in LVEF to below the lower limit of normal (<50%).
- Techniques such as GLS may even detect subclinical LV dysfunction; >15% ↓ from baseline is abnormal.

Cardiac MRI

- *Pros:* reproducible, enables assessment of cardiac structure and haemodynamics, no radiation, tissue characterization (detection of myocarditis, fibrosis, etc.) by using T1/extracellular volume (ECV)/T2 mapping techniques.
- *Cons:* cost, limited availability, requirements of patient (claustrophobia, breath-hold, acquisition time).

Nuclear cardiac imaging

- *Pros:* reproducible for LVEF.
- *Cons:* radiation, little information on cardiac structure and function.

Functional testing and coronary imaging

- Perfusion MRI, stress echocardiography, nuclear imaging, CTCA, and invasive coronary angiography are among some of the modalities that may be used to assess patients for CAD if required.

Assessment of peripheral arterial disease

- The ABPI should be performed in patients where PAD may be worsened by the planned chemotherapeutic agent.

Newer echocardiographic assessment techniques

- LVEF represents longitudinal, radial, and circumferential strain. Deterioration in one form of contractility compensated by others is common. Thus, LVEF is not a sensitive marker of cardiac function.
- Historically, LVEF has been calculated by using Simpson's biplane method. More recently, three-dimensional echocardiography has been shown to be more reproducible and is comparable to values obtained by MRI.
- Strain, which measures myocardial deformation, has been proposed as a means to identify cardiac involvement prior to EF changes. At present, a >15% ↓ in GLS from baseline is abnormal.
- In the SUCCOUR trial, individuals on potential cardiotoxic chemotherapy were randomized to GLS- vs LVEF-guided cardioprotective management. Although the overall change in LVEF was no different between the two arms, when those received cardioprotective therapy were compared, a GLS-guided approach resulted in a significantly lower reduction in LVEF at 1 year.

General principles of management and prevention of cardiotoxic effects

Left ventricular dysfunction

- There are limited data, in the cardio-oncology context, on the use of drugs known to have prognostic benefits in HF patients. Therefore, use of β-blockers and ACEis is currently unlicensed.
- While the benefits of these therapies in cancer patients have been shown in trials such as the Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research (MANTICORE) and Prevention of Cardiac Dysfunction during Adjuvant Breast Cancer Therapy (PRADA), further generalizable data are required before guideline changes for routine prophylactic cardioprotection.
- Moreover, the SAFE-HEaRt pilot study examined the cardiac safety of HER2-targeted therapy in patients with reduced LV function, suggesting that asymptomatic patients with reduced LV systolic function (LVEF 40–50%) can continue to receive HER2 inhibitors, with regular follow-up, ACEis, and β-blockers.
- Dexrazoxane should be considered to reduce the risk of HF in those treated with anthracyclines.

Coronary artery disease

- Given that a large proportion of cancer therapies can cause thrombocytopenia, this poses a particular problem in individuals with CAD.
- As a general rule, the shortest duration of antiplatelet therapy should be considered.

Valvular heart disease

- Cardiac surgery may be difficult in those who have had radiotherapy due to mediastinal fibrosis. Therefore, transcatheter valve implantation may provide a more attractive option.

Pericardial disease

- Acute pericarditis is usually managed with NSAIDs and colchicine; pericardiocentesis may be required if there is a large effusion.

Arrhythmias

- QTc >500ms or an absolute ↑ of ≥60ms from baseline is considered higher risk for the development of torsades de pointes.
- Treatment in this case should be interrupted, and electrolyte levels assessed and corrected if necessary. Treatment may be resumed at a reduced dose when the QTc is corrected.

Atrial fibrillation/flutter, deep vein thrombosis, and pulmonary embolism

- Vitamin K antagonists (VKAs) are generally avoided for anticoagulation, particularly in those with metastatic disease or a high bleeding risk according to the HASBLED score.
- LMWH is preferable in this case.
- NOACs may also be safer than VKAs; however, further work is required. There have been no head-to-head comparisons between LMWH and DOACs.
- A vena cava filter may be considered if anticoagulation is failing or contraindicated.

Hypertension

- Hypertension should be treated promptly.
- Generally, β-blockers or ACEis and dihydropyridine CCBs are preferred, as non-dihydropyridine CCBs can ↑ certain drug plasma levels due to their action on cytochrome P450 3A4.

Myocarditis

- Myocarditis secondary to checkpoint inhibitors occurs in 1% of individuals; however, registry data suggest mortality of 40–50%.
- Treatment is with high-dose IV steroids. In the event that steroids are ineffective, tacrolimus and/or mycophenolate mofetil may be administered. IV immunoglobulins and plasmapheresis should be considered where tacrolimus/mycophenolate mofetil have failed.
- Due to the irreversible nature of checkpoint inhibitors, troponin levels may remain elevated for >1 year.

Follow-up of early and late effects of cancer therapy

The precise frequency and timing of investigations are largely based on consensus recommendations and is determined by the choice of agent. This varies from document to document. The recommendations below follow the 2016 ESC position paper on cancer treatments and CV toxicity developed under the auspices of the ESC Committee for Practice Guidelines.[1]

General strategies

Cardiac function assessment should be performed at baseline, during therapy, and after treatment completion. If the baseline risk is high (see Box 11.1), the frequency of follow-up may be ↑ during treatment.

ECG

- In individuals known to be taking an agent which ↑ the QT interval, an ECG should be repeated a week after any change in dose, monthly for the first 3 months, and then at a frequency dependent on the patient and drug.

Echocardiography

- In those with significant ↓ in LVEF of >10% to a value below the lower limit of normal (<50%), ACEis and β-blockers are recommended, especially if there is a concomitant significant drop in GLS (although currently unlicensed). Individuals whose EF falls >10% to a value above the lower limit of normal should undergo more frequent assessment of LV function. In those in whom cardiotoxic effects are detected, long-term surveillance should be considered.
- When using chemotherapeutic agents which can induce PHT, NYHA functional class and pulmonary pressures should be assessed every 3 months.

Anthracyclines

- Cardiac function should be assessed at baseline, then at 3-monthly intervals and at the end of treatment. In those individuals with higher doses of anthracyclines (cumulative dose of 240mg/m^2), additional monitoring with biomarkers may be considered, especially in those with CV risk factors. Those exposed to high cumulative doses should be offered lifelong surveillance.

Human epidermal growth factor receptor 2 inhibitors

- Cardiac function should be assessed at baseline, every 3 months during treatment, and once after treatment.

Vascular endothelial growth factor inhibitors

- Cardiac function should be assessed at baseline and at regular intervals, depending on the drugs and sequence of treatments.

Radiotherapy

- Valvular surveillance should be performed a decade post-radiation and then 5-yearly following this. Evaluation of CAD is recommended following radiation to the mediastinum at around 5 years and then 5-yearly following this.

Reference

1. Zamorano JL, Lancellotti P, Muñoz DR, *et al*.; ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;**37**:2768–801. Available from: 🖱 https://doi.org/10.1093/eurheartj/ehw211

Further reading

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Chung R, Ghosh AK, Banerjee A. Cardiotoxicity: precision medicine with imprecise definitions. *Open Heart*. 2018;**5**:e000774. doi:10.1136/openhrt-2018-000774.

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Chapter 12

Cardiac investigations

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Exercise ECG

- A commonly used test involving a treadmill, BP measurement, and continuous ECG.

Indications

- Diagnosis of CAD: given its comparative poor sensitivity (68%) and specificity (77%), exercise ECG may be considered if alternative imaging is not available.
- To assess prognosis, functional capacity, and therapy response in those with CAD or conditions associated with HF.
- To assess patients with symptoms of arrhythmia during exercise.
- To assess functional capacity in VHD or CHD.
- To assess patients with rate-responsive pacemakers.

Contraindications

Absolute

- Acute myocardial infarction <2 days
- Unstable angina
- Uncontrolled symptomatic/haemodynamically compromising arrhythmias
- Symptomatic severe aortic stenosis
- Uncontrolled symptomatic heart failure
- Acute myocarditis
- Acute pulmonary embolism
- Acute aortic dissection

Relative

- Known left main stem stenosis
- Uncontrolled raised BP (systolic >180mmHg and/or diastolic >100mmHg)
- Outflow tract obstruction (e.g. hypertrophic cardiomyopathy)

Cautions and causes of false-positive tests

- In patients with an ECG abnormality rendering interpretation of ST-segment difficult (e.g. LBBB, LVH with strain, or ECG changes secondary to digoxin), alternative modalities of assessment should be sought.
- Cardiomyopathies.
- Hypertension.
- Electrolyte abnormalities.
- Coronary artery spasm.

Principles of exercise testing

- *ECG leads:* chest electrodes are placed as per standard 12-lead ECG. Arm electrodes are placed 2cm below the clavicular fossa (left/right side). Leg electrodes are placed on the lateral torso midway between the costal margin and the iliac crest (left/right side).
- *BP cuff:* should also be placed on the upper arm.

- *Bruce protocol:* standardized protocol used during exercise testing, which comprises seven stages, each lasting 3min.
- *Modified Bruce protocol:* typically used in elderly or more sedentary patients; adds two warm-up stages to the standard protocol.
- *BP and ECG measurements:* should take place at baseline, prior to progression to the next stage, and at 1min intervals in recovery.

When to stop the test

- Target heart rate achieved—better sensitivity and specificity if the target heart rate (>85% of age-predicted) is reached
- Worsening angina
- Excessive breathlessness
- Dizziness
- Fatigue/patient requests to stop
- Atrial arrhythmia other than ectopic beats
- Cyanosis/pallor
- Frequent ventricular ectopics or ventricular tachycardia
- Worsening ST-segment shift (elevation or depression) (see Fig. 12.1)
- BP fall (>20mmHg) or failure to rise
- Exaggerated hypertensive response (BP >230mmHg)
- New high-grade atrioventricular block or bundle branch block

Criteria for a positive test

- Planar or downsloping ST-segment depression of ≥1mm 80ms after the J point (junction between the QRS and ST-segment) (see Fig. 12.1).
- ST-segment elevation (>1mm in leads without diagnostic Q waves, other than leads V1/aVR).
- Failure of BP to rise during exercise.
- Ventricular arrhythmias.
- Typical ischaemic symptoms during exercise.
- Inability to ↑ HR.

Duke Treadmill Score

- Can provide prognostic information in those without known CAD.
- Duke Treadmill Score (DTS) = exercise time (min) − [5 × ST-segment deviation (mm)] − [4 × angina index*], where *0 = no angina, 1 = angina during test/recovery, and 2 = angina is the reason for stopping the test.
- A score of ≥5: 4-year survival is 99%—the patient may be managed medically. If the score is <−10, 4-year survival is 79%—these patients should be referred for coronary angiography.

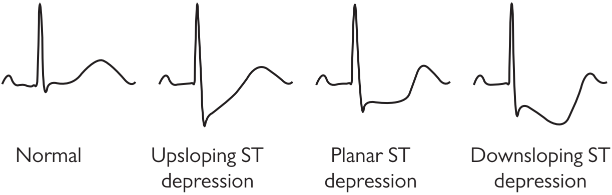

Fig. 12.1 Depiction of possible ST-segment changes during exercise testing.

Transthoracic echocardiography: physics

Introduction

- Echoreflection was developed by Edler and Herz in the 1950s and was first implemented clinically in the 1960s. Echocardiography is still the mainstay of assessment of cardiac morphology and function.
- Competent interpretation of the echocardiographic examination first requires an understanding of the principles underlying the technique.

Ultrasound physics

Ultrasound

- Sound waves travel in a longitudinal manner by means of compression (waves closer together) and rarefaction (waves further apart).
- *Amplitude:* difference between the peak and average pressure measured in decibels (dB). This is a measure of strength of the signal.
- *Wavelength:* the distance between two waves (peak-to-peak or trough-to-trough) measured in metres (m).
- *Frequency:* the number of wave cycles in each second measured in hertz (Hz)—a frequency of >20,000Hz is characterized as US.
- Propagation speed = wavelength × frequency. The average speed in soft tissue is 1540m/s. This is higher in bone and lower in air. This speed is used to calculate the distance of a structure.

Components of the transducer

- *Transducer:* US is generated by a transducer, which is both a receiver and a transmitter. This comprises an acoustic lens, a matching layer, piezoelectric elements, and a backing layer (see Fig. 12.2).
- *Piezoelectric effect:* certain crystals change shape when exposed to an electric current. By applying a rapidly alternating current, such crystals can be made to oscillate and generate US. Similarly, when exposed to US, the crystals will oscillate and generate an electric current, which can be detected as a signal.
- *Backing layer:* the piezoelectric elements are mounted on a backing layer. This absorbs US and dampens crystal reverberation.

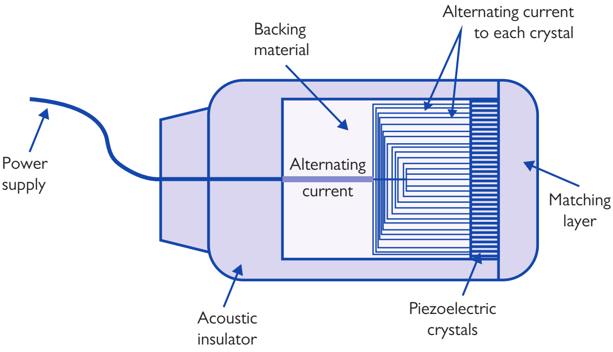

Fig. 12.2 Components of a transducer.

- *Matching layer*: serves to improve impedance matching between the piezoelectric elements and the body.
- *Acoustic lens:* helps to focus the US beam.

Mechanism of action

- *Transmitting and receiving US:* short bursts of US are transmitted, followed by a pause, while the reflected US returns before the next burst is transmitted. The US beam generated has a natural focus point and then progressively ↑ width due to diffraction. The beam is therefore divided into the near field and the far field.
- *Spatial resolution:* as the velocity of sound is constant within a medium, object location is determined based on the timing of the returning signal.
- *Attenuation:* as US travels through tissue, it can attenuate. This is due to absorption, but also due to reflection and scatter. Attenuation ↑ the further US travels and with US frequency.
- The amplitude of the returning signal is based on the angle of incidence (surfaces perpendicular to the US beam are stronger reflectors) and the interface of acoustic impedances. At smooth and large interfaces (larger than the wavelength of sound), such as in the LV at the tissue–blood interface, there is greater reflectivity; at a rough interface/small structures (similar to the wavelength of sound), US is scattered in many different directions.
- Returning US information is mapped to pixels for display and digital storage.

Transthoracic echocardiography: artefacts

- *Reverberation:* this is seen when the beam bounces between two reflectors before it returns to the transducer. The US signal can therefore be interpreted as having come from further away than it has and can lead to ghost images in the far field.
- *Acoustic shadowing:* a structure (e.g. bone) may be highly reflective and therefore prevent the US from travelling any further. This can prevent structures behind highly reflective structures from being seen.
- *Beam width artefact:* this occurs when the transducer cannot tell whether the returning signal has come from the centre or the edge of the beam and can lead to smearing of the image.

TTE: modes of imaging

M-mode

- This was the first available form of echocardiography.
- M-mode records motion along a single line, providing motion display (*y*-axis) against time (*x*-axis).
- Due to the narrow field of view, there is a very high sampling rate, which makes this mode very useful for visualizing rapid motion (e.g. valve leaflets opening and closing) (see Fig. 12.3).

Two-dimensional imaging

- *Scanning:* when a US beam is swept across a cardiac window, rapid sequential sampling can be performed, leading to display of multiple 'scan lines' of information.
- *Interpolation:* since a finite number of scan lines is possible, interpolation of data between lines is performed and a frame is stored in digital form.
- *Reiterative acquisition:* over a cardiac cycle, a movie composed of sequentially acquired frames is created, demonstrating structural motion, which can then be displayed on a monitor.
- *Frame rate:* the probe has to transmit and receive US for each scan line, limiting how many frames are generated per second. Reducing the sector width reduces the time taken to generate a frame, thereby ↑ the number of frames per second (frame rate).
- *Harmonics:* harmonic tissue imaging has substantially improved image resolution by eliminating artefactual 'noise'. Low-level signals emanating from tissue and comprising the first harmonic of the transmitted US are selectively sampled. In this way, extraneous reflections, such as reverberations, are filtered out, leaving a cleaner image.

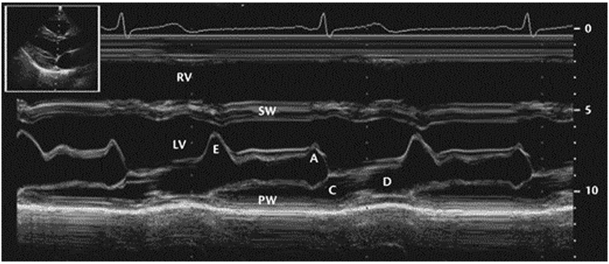

Fig. 12.3 M-mode of the mitral valve. A, atrial contraction causes late diastolic peak in leaflet movement; C, both leaflets join in middle of cavity; D, leaflets start separation; E, maximum anterior movement of the anterior leaflet; LV, left ventricle; PW, posterior wall of left ventricle; RV, right ventricle; SW, septal wall of left ventricle.

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Three-dimensional imaging

Left ventricular volumes and function

- 3D echocardiography has a distinct advantage over 2D echocardiography in that there is no geometrical assumption made about the LV and there is no foreshortening of the LV apex.
- 3D echocardiography has been used to estimate LV mass and RV size and function, as well as atrial volumes.
- However, the need for high-quality images for volumetric assessment has limited its use thus far.

Structural heart disease

- 3D TOE of the MV has enabled visualization in a multitude of planes, enabling accurate assessment of aetiology and surgical planning.

Percutaneous structural heart disease

- 3D echocardiography has been used to guide procedures such as closure of PFOs, mitral valvuloplasty, and left atrial appendage (LAA) cclude device insertion.
- A new system (EchoNavigator®) enables the superimposing of soft structures over the cardiac shadow. This may be used to guide percutaneous intervention in the near future.

TTE: Doppler

Principles

- Sound waves from a source moving towards an observer shorten in wavelength (higher frequency) in the direction of its movement.
- This phenomenon occurs in blood cells. Those moving towards the transducer create higher frequency in the returning US than those moving away.
- The change in frequency between the transmitted and returning signal is known as the Doppler shift, from which the velocity of red blood cells may be calculated.
- The beam must be as parallel as possible to the target, with off-axis angulation by >30° leading to significant underestimation of velocities.

Spectral Doppler

- *Doppler shift:* the difference between transmitted and returning US frequencies is calculated for the returned signal, which contains a spectrum of frequencies.
- *Display:* can be plotted as time (*x*-axis) vs velocity (*y*-axis). Flow that is towards the transducer is positive. The signal density represents the number of red blood cells moving at that velocity.
- *Gain:* may be used to ↑ the signal. The baseline and range of velocities can also be altered to optimize the trace.

Pulsed-wave Doppler

- Pulsed-wave (PW) Doppler permits accurate sampling of blood velocities within a limited region of interest or ‘sample volume’ (see Fig. 12.4).
- The transducer transmits a pulse of US and then samples the US from the point of interest.

Nyquist limit

- To measure a wavelength, the waveform must be sampled twice per cycle. When using pulsed-wave Doppler, the transducer has to wait for the US to return. This limits when it can send out the next set of US pulses. This is the pulse repetition frequency (PRF).
- The further the region of interest is from the probe, the longer the US signal takes to return and the ↓ the PRF. This limits the Doppler shift that can be measured and is equal to 50% PRF (*Nyquist limit*).
- Once the velocity of blood exceeds this limit then aliasing occurs and the waveform top is missing on the spectral doppler display.

Continuous-wave Doppler

- This uses different crystals to transmit and receive. Unlike PW Doppler, CW Doppler uses continuous US transmission and reception.
- Signals are taken from the entire length of the beam. A virtual cursor positioned over the 2D image can be moved to guide and minimize off-axis sampling angulation.
- CW Doppler cannot be used to assess flow at a single point. However, it can measure higher velocities without aliasing. This enables assessment of velocities found in stenotic and regurgitant lesions (see Fig. 12.5).
- CW Doppler can be performed with stand-alone (Pedoff) probes (e.g. in the assessment of AS).

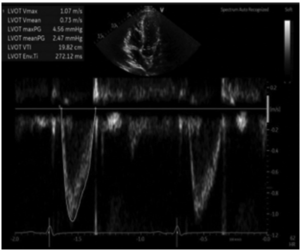

Fig. 12.4 Pulsed-wave Doppler of the left ventricular outflow tract.

Image courtesy of Paulo Bulleros.

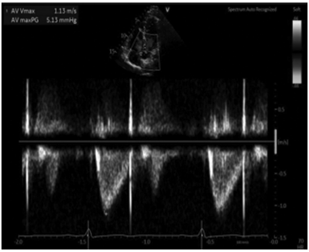

Fig. 12.5 Spectral Doppler of the aortic valve.

Image courtesy of Paulo Bulleros.

Colour Doppler

- This portrays blood flow overlying the 2D image.
- Colour Doppler is used to detect stenotic/regurgitant lesions or shunts, and qualitative assessment is possible by using colour maps.
- Pixels are assigned a colour, based on user-configurable mapping parameters and on average velocity in the region of interest.
- By convention, the BART colour map system is used in all machines: *b*lue colour represents flow *a*way from the transducer and *r*ed colour depicts flow *t*owards the transducer.
- The lighter the colour, the higher the velocity. Abnormal velocity distributions characteristic of turbulence can be mapped, usually by including a green hue ('variance mapping').
- Aliasing is depicted as a mix of colours or a 'mosaic' pattern.

Tissue Doppler

- This is used to assess low-velocity displacement of structures. A high-pass filter excludes higher-frequency shifts caused by red cell flow, leaving only low-velocity shifts attributable to wall motion.
- Mitral or tricuspid annular motion can be tracked and correlates with systolic and diastolic performance of the associated ventricles.
- Regional wall motion can be assessed for displacement, which may be affected by overall cardiac motion or local tethering.

TTE: standard views

- A comprehensive examination should include M-mode, spectral Doppler, colour Doppler, and tissue Doppler.
- Standard scanning positions are shown in Fig. 12.6.

Parasternal views

Parasternal long axis view

- The patient should be positioned onto their left-hand side, with their left arm behind their head.
- The transducer is placed (the probe's reference point/dot pointing towards the right shoulder) in the third/fourth ICS.
- *Structures:* see Fig. 12.7.
- *Colour flow:* across MV and aortic valve.
- *Measurements:* interventricular septum (IVS) (end-diastole), LV posterior wall thickness (LVPWT) (end-diastole), LVEDD (end-diastole), LVESD (end-systole), LA (end-systole), aortic annulus (end-diastole), LVOT (mid systole), and RVOT (end-diastole) diameters (with 2D or M-mode).

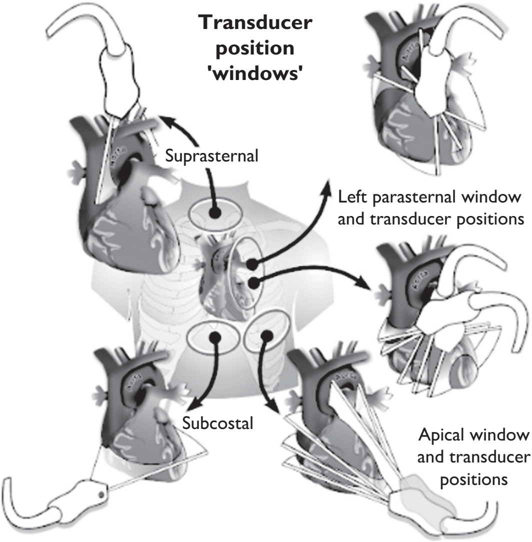
Transducer position 'windows'
Suprasternal
Left parasternal window and transducer positions
Subcostal
Apical window and transducer positions
Aorta

Fig. 12.6 Standard scanning positions.

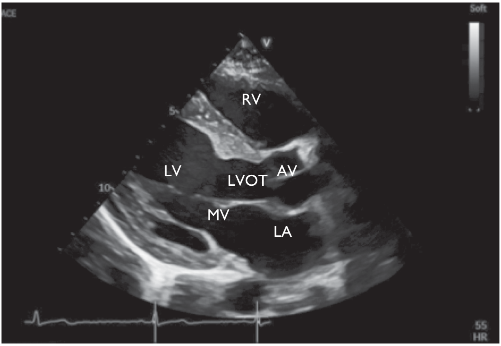

Fig. 12.7 PLAX view. AV, aortic valve; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; MV, mitral valve; RV, right ventricle.

Image courtesy of Paulo Bulleros.

Right ventricular outflow view

- This view is obtained by tilting the probe (all movements in this chapter refer to movement of the head of the probe in contact with the patient) laterally and cranially (towards the patient's left shoulder).
- *Structures:* see Fig. 12.8.
- *Colour flow:* across PV (may be able to detect PDA jet).
- *Measurements:* main PA, left and right PA diameters, CW and PW of PV for assessment of PV inflow/regurgitation and PV acceleration time, used as an additional measure of pulmonary arterial systolic pressure (PASP), respectively.

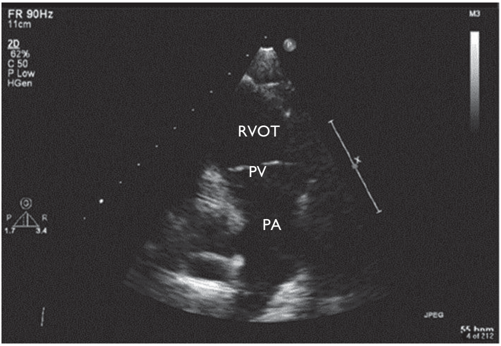

Fig. 12.8 Right ventricular outflow view. PA, pulmonary artery; PV, pulmonary valve; RVOT, right ventricular outflow tract.

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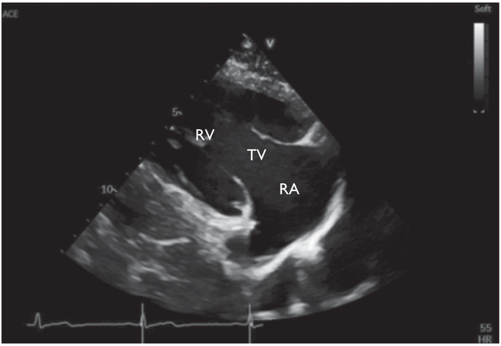

Fig. 12.9 Right ventricular inflow view. RA, right atrium; RV, right ventricle; TV, tricuspid valve.

Image courtesy of Paulo Bulleros.

Right ventricular inflow view

- This view is obtained by tilting the probe medially and caudally (towards the patient's right hip).
- *Structures:* see Fig. 12.9.
- *Colour flow:* across TV.
- *Measurements:* CW of TV for assessment of TV inflow/regurgitation.

Parasternal short axis view

- This view is obtained by rotating the probe from its position in the PLAX, so that it points towards the patient's left shoulder.
- There are four views within the PSAX: aortic level, MV level, papillary muscle level, and apical level (see Fig. 12.10).
- The views are obtained by tilting the probe along the axis of the heart.

Aortic level

- *Structures:* see Fig. 12.10a.
- *Colour flow:* across IAS, aortic valve, TV (may be able to detect PDA), and PV.
- *Measurements:* RVOT1, RVOT2, CW of TV, CW and PW of PV.

Mitral valve level

- *Structures:* see Fig. 12.10b.
- *Colour flow:* across MV and IVS.
- *Measurements:* MV area (if MS present, measured in mid diastole at the tip of the MV leaflets), LV wall thickness (LVWT) (end-diastole)—anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral.

Papillary muscle level

- *Structures:* see Fig. 12.10c.
- *Colour flow:* across IVS.
- *Measurements:* LVWT (end-diastole)—anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral.

Apical level

- *Structures:* see Fig 12.10d.
- *Colour flow:* n/a
- *Measurements:* LVWT (end-diastole)—anterior, inferior, septal, and lateral

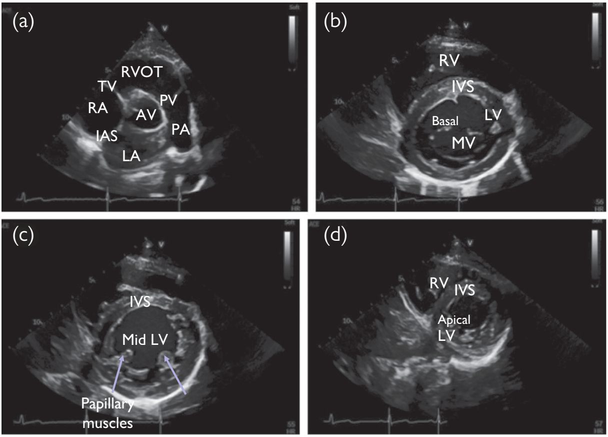
(a)
RVOT
TV
RA
AV
PV
PA
IAS
LA
(b)
RV
IVS
Basal
LV
MV
(c)
IVS
Mid LV
Papillary muscles
(d)
RV
IVS
Apical
LV

Fig. 12.10 PSAX view. (a) Aortic level. (b) Mitral valve level. (c) Papillary muscle level. (d) Apical level. AV, aortic valve; IAS, inter atrial septum; IVS, inter ventricular septum; LA, left atrium; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; TV, tricuspid valve.

Image courtesy of Paulo Bulleros.

Apical window

Four-chamber (4Ch)

- This view is obtained by placing the probe in the apical position (fifth ICS in the mid-clavicular line), with the probe directed towards the patient's left-hand side.
- One should take care not to foreshorten the image. This occurs where the plane of the US does not pass through the true apex. The apex therefore looks rounded rather than bullet-shaped.
- *Structures:* see Fig. 12.11a.
- *Colour flow:* across MV, TV, IAS, and IVS.

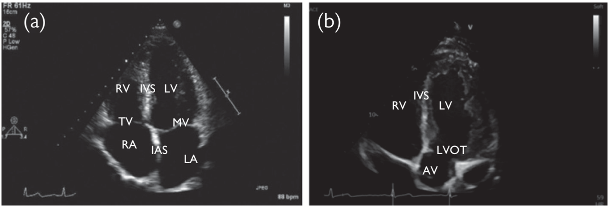
(a)
RV
IVS
LV
TV
MV
RA
IAS
LA
(b)
IVS
RV
LV
LVOT
AV

Fig. 12.11 (a) Four-chamber view. (b) Five-chamber view. AV, aortic valve; IAS, inter atrial septum; IVS, inter ventricular septum; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.

Image courtesy of Paulo Bulleros.

- *Measurements:* LA area and volume, RA area, modified Simpson's method to assess LV function (see ➔ TTE: left ventricular systolic function, p. 502), CW of TV, MV for assessment of inflow/regurgitation, LV inflow—PW (level of MV tips), PW pulmonary veins for assessment of flow, tissue Doppler imaging (TDI) of mitral annulus and tricuspid annulus, RV dimensions (basal, mid, and longitudinal at end-diastole), tricuspid annular plane systolic excursion (TAPSE) for assessment of RV function. If MR, measure proximal isovelocity surface area (PISA) and vena contracta (VC) (see ➔ Proximal isovelocity surface area and vena contracta, p. 509).

Five-chamber (5Ch)

- This view is obtained by angling the probe anteriorly.
- *Structures:* see Fig. 12.11b.
- *Colour flow:* across aortic valve.
- *Measurements:* PW of LVOT, CW of AV for assessment of inflow and regurgitation. If AR, measure VC and pressure half-time.

Two-chamber (2Ch)

- This view is obtained by rotating the 4Ch position of the probe anticlockwise through 60°. The probe should be facing the patient's left shoulder.
- *Structures:* see Fig. 12.12a.
- *Colour flow:* across MV.
- *Measurements:* modified Simpson's method to assess LV function, CW of MV, LA area and volume.

Three-chamber (3Ch)

- This view is obtained by rotating the 2Ch position of the probe further anticlockwise through 60°.
- *Structures:* see Fig. 12.12b.
- *Colour flow:* across MV, across AV.
- *Measurements:* CW of MV and AV.

Subcostal window

- This view is obtained by lying the patient flat. The probe, directed leftwards, is then placed below the xiphisternum and angled up to the heart.
- *Structures:* as for 4Ch (see Fig. 12.13a).
- *Colour flow:* as for 4Ch.
- *Measurements:* RV wall (end-diastole).

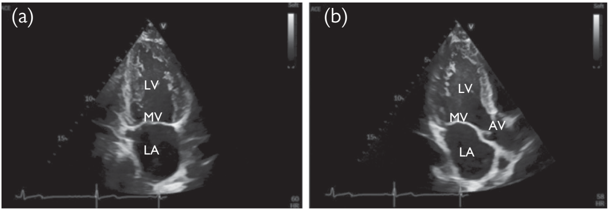

Fig. 12.12 (a) Two-chamber view. (b) Three-chamber view. AV, atrial valve; LA, left atrium; LV, left ventricle; MV, mitral valve.

Image courtesy of Paulo Bulleros.

Subcostal inferior vena cava inflow

- This view is obtained by rotating the probe 90°.
- *Structures:* see Fig. 12.13b.
- *Colour flow:* n/a.
- *Measurements:* IVC in inspiration and expiration.

Suprasternal window

- This view is obtained by asking the patient to raise their chin, in the supine position. The probe is placed in the suprasternal notch, with the reference point/dot cranially, and angled downwards.
- *Structures:* see Fig. 12.14.
- *Colour flow:* across aorta (may be able to detect PDA jet).
- *Measurements:* CW of aorta for assessment of flow in the descending aorta.

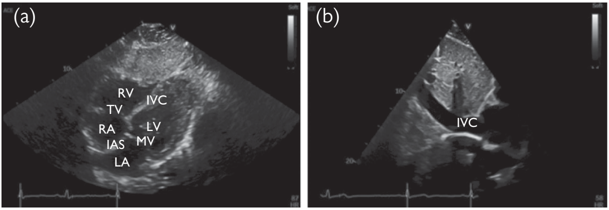
(a)
RV
IVC
TV
RA
LV
IAS
MV
LA
(b)
IVC

Fig. 12.13 (a) Subcostal window. (b) Subcostal inferior vena cava inflow. IAS, inter atrial septum; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.

Image courtesy of Paulo Bulleros.

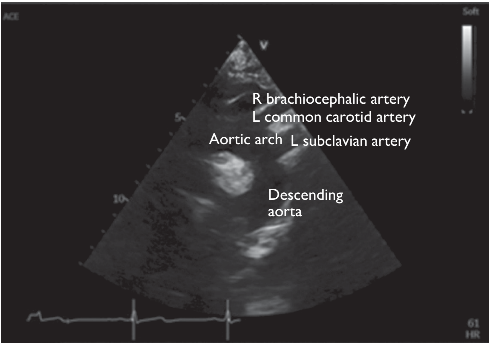
R brachiocephalic artery
L common carotid artery
Aortic arch
L subclavian artery
Descending aorta
61
HR

Fig. 12.14 Suprasternal window.

Image courtesy of Paulo Bulleros.

TTE: standard measurements

- Measurements are usually taken in relation to systole and diastole.

- *End-diastole:* onset of the QRS complex
- *End-systole:* just prior to mitral valve opening

Ventricular evaluation

Left ventricle

Dimensions

- IVS, LVEDD, and LVPWT are measured in PLAX at end-diastole, in line with MV tips. LVESD is measured at end-systole.

Volumes

- LV volumes are measured by using 2D or 3D echocardiography.
- The endomyocardial border is traced in end-systole and end-diastole. The contour is closed at the mitral ring with a straight line. The LV length is defined as the centre of this line to the apex (see Fig. 12.15).
- The modified Simpson's biplane method of disc summation is then applied (see ➔ TTE: left ventricular systolic function, p. 502).

Function

(See ➔ TTE: left ventricular systolic function, p. 502.)

Derived variables

- *Fractional shortening (FS):* this is a measure of the percentage change in the LV between diastole and systole.

$$\mathrm{FS} = (\mathrm{LVEDD} - \mathrm{LVESD}) / \mathrm{LVEDD}.$$

- *Mass:* can be calculated as:

$$\text{LV mass} = (0.8 \times (1.04 \times ((\mathrm{LVEDD} + \mathrm{LVPWD} + \mathrm{IVSD})^3 - \mathrm{LVEDD}^3)) + 0.6$$

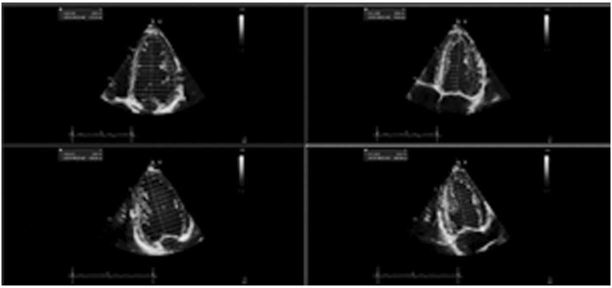

Fig. 12.15 Simpson's biplane method.

Image courtesy of Paulo Bulleros.

Right ventricle

Dimensions

- Size measured in the 4Ch view in end-diastole at the base (RVD1) mid level (RVD2), and longitudinally from the base–apex (RVD3).
- Wall thickness measured in subcostal view (end-diastole); RVH >5mm.

Function

- RV fractional area change (FAC) is calculated by measuring the RV area at end-systole and end-diastole in the 4Ch view.

$$\text{RVFAC} = \left(\left(\text{end-diastolic area} - \text{end-systolic area}\right) / \text{end-diastolic area}\right) \times 100$$

- TAPSE is measured by placing the cursor so that it passes through the lateral side of the tricuspid annulus by using M-mode. The vertical displacement of the annulus in systole is then measured.

Ventricular outflow tract

- *LVOT*: the LVOT diameter is measured in the PLAX view in mid systole at the aortic annulus.
- *RVOT*: the RVOT is measured in the PSAX view at the aortic valve level (RVOT1) and PV annulus level (RVOT2) (see Fig. 12.16).

Atrial evaluation

Left atrium

- The LA is measured at end-systole in the PLAX view.
- The LA area is traced at end-systole in the 4Ch and 2Ch views.
- The LA volume is calculated by using modified Simpson's biplane method of discs (see ➔ TTE: left ventricular systolic function, p. 502).

Right atrium

- The RA area is traced at end-systole in the 4Ch view.

Aortic evaluation

- The aortic root is measured at cuspal level, and the aorta is measured at the sinotubular junction and 2cm above this in end-diastole.

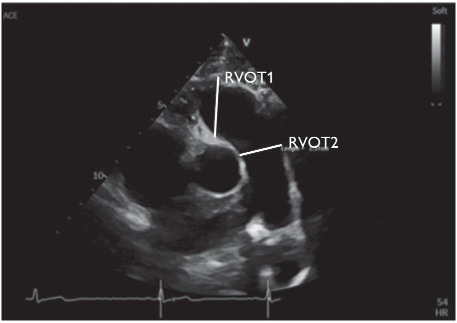

Fig. 12.16 Right ventricular outflow tract measurements in the PSAX view.
Image courtesy of Paulo Bulleros.

TTE: assessment of wall motion

- Various labelling systems have been used when describing the LV, but the AHA Cardiac 17-segment model is the standard convention (see Fig. 12.17):
- *Basal* (6): anteroseptal, anterior, anterolateral, inferolateral, inferior, and inferoseptal
- *Mid LV* (6): anteroseptal, anterior, anterolateral, inferolateral, inferior, and inferoseptal
- *Apical* (5): anterior, lateral, inferior, septal, and true apical.

Regional functional assessment

- *Overall systolic function:* should be classified as 'normal', 'globally hypokinetic', or demonstrating the presence of 'RWMAs'.
- *Segments:* can each be described as hyperkinetic/normal/hypokinetic/akinetic/dyskinetic. Normal segments thicken by >50% during systole.
- *Scarring:* suggested by hyperechogenic, thinned areas. Scarred segments may demonstrate endocardial motion, without wall thickening, due to tethering by peripheral segments.

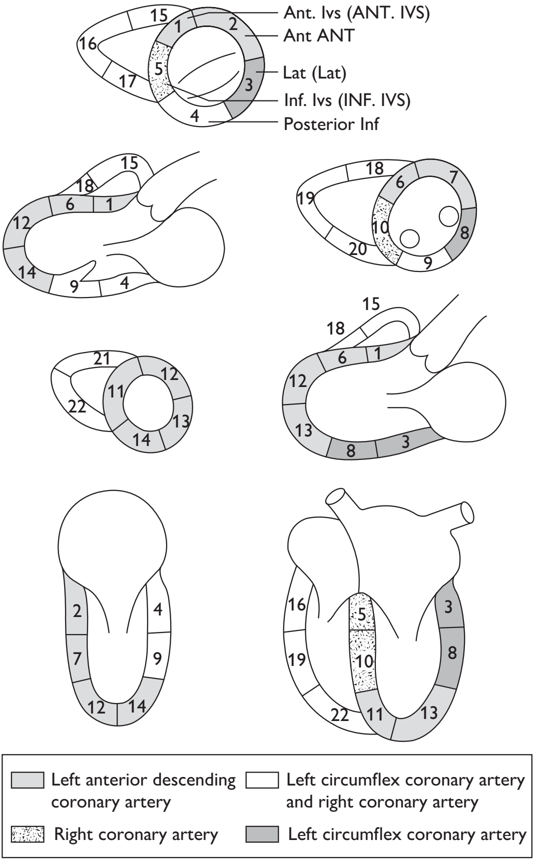
15
1
2
16
5
17
3
4
Ant. Ivs (ANT. IVS)
Ant ANT
Lat (Lat)
Inf. Ivs (INF. IVS)
Posterior Inf
15
18
6
1
12
14
9
4
18
6
7
19
10
8
20
9
15
18
6
1
21
12
11
22
13
14
12
13
8
3
2
4
7
9
12
14
16
5
3
19
10
8
22
11
13
Left anterior descending coronary artery
Left circumflex coronary artery and right coronary artery
Right coronary artery
Left circumflex coronary artery

Fig. 12.17 American Heart Association 17-segment model.

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TTE: left ventricular systolic function

Global functional assessment

- 2D echocardiographic EFs can be quantified most efficiently by using the Simpson's modified biplane method of stacked discs.
- However, in scans with reduced quality where using the Simpson's modified biplane method is not possible, or likely to be inaccurate, a trained eye is usually the best estimate of EF (see Table 12.1).

Simpson's modified biplane method

- *Division of the LV:* 4Ch and 2Ch LV traces are performed and the apex–annulus length is divided into a standard number of equal segments, the length of which serves as disc height.
- *Disc area:* the cross-sectional disc area is calculated from the elliptical formula ($\pi r_1 r_2$), where r_1 and r_2 = the endocardial medial–lateral dimension of each segment in the 4Ch and 2Ch views, respectively.
- *Total volume:* the volumes of each disc are added together to give the end-diastolic and end-systolic volumes, from which the EF is calculated.

$$\mathrm{EF} = (\mathrm{LVEDV} - \mathrm{LVESV}) / \mathrm{LVEDV} \times 100$$

Global longitudinal strain

- GLS is a measure of deformation that is assessed by using speckle tracking echocardiography (see ➔ TTE: strain imaging, pp. 512–13).
- It measures the change in length of the myocardium between end-diastole and end-systole relative to the end-diastolic length.
- GLS is more sensitive to subtle changes in LV function.
- A GLS of −20% is considered normal; however, normal values may be dependent on the vendor.

Table 12.1 Assessment of left ventricular ejection fraction

Left ventricular ejection fraction (%)	Qualitative assessment
>75	Hyperdynamic
55–75	Normal
50–54	Low-normal
36–49	Impaired
≤35	Severely impaired

TTE: left ventricular diastolic function

- Diastolic function reflects impaired LV relaxation.

Left atrial enlargement

- LA enlargement suggests ↑ LV filling pressures as a possible cause.

Pulsed-wave Doppler mitral inflow

- E wave (peak early diastolic velocity), A wave (peak atrial systolic velocity), E/A ratio, E wave deceleration time (DT).
- The DT is the time between the beginning and end of the E wave and is normally 150–200ms. Fig. 12.18 demonstrates the utility of the E and A waves in grading of diastolic dysfunction.
- The following should be taken into account when assessing these parameters:

> - E/A ratio is particularly dependent on sample volume placement and loading conditions.
> - E/A ratio ↓ with age, and assessment must be age-normalized. An E/A ratio of <1.0 is common among the elderly and often represents normal ageing.

Isovolumetric relaxation time

- The isovolumetric relaxation time (IVRT) is the time between aortic valve closure and MV opening, and is normally 50–100ms. This is prolonged in diastolic dysfunction.
- This is measured by using PW Doppler at the junction between LV inflow and outflow in the 4Ch view.

Pulsed-wave Doppler of pulmonary veins

- Flow into the LA can be sampled.
- Pulmonary vein flow is made up of the S, D, and A waves.
- By using PW Doppler, the peak systolic (S wave) velocity (PV_S), peak diastolic (D wave) velocity (PV_D), peak atrial reversal velocity (PV_a), and duration of atrial reversal (a_{dur}) can be obtained.
- Normally, $PV_S > PV_D$; PV_a is <0.35m/s.
- a_{dur} is <20ms longer than the duration of the A wave measured on LV inflow.
- PV_a and a_{dur} are ↑ if LVEDP is ↑.

Tissue Doppler of medial and lateral mitral annuli (E′, A′)

- Sample the septum and lateral wall 1cm below (towards the apex) the mitral annulus.
- E′ corresponds to early relaxation of the LV, and A′ corresponds to atrial contraction (see Fig. 12.19).
- The E/E′ ratio correlates roughly with LVEDP; a ratio of >15 is strongly suggestive of elevated filling pressure, and a ratio of <8 is strongly suggestive of normal filling pressure.
- Fig. 12.20 summarizes how to approach a patient with LV diastolic dysfunction and corresponding grades of dysfunction.

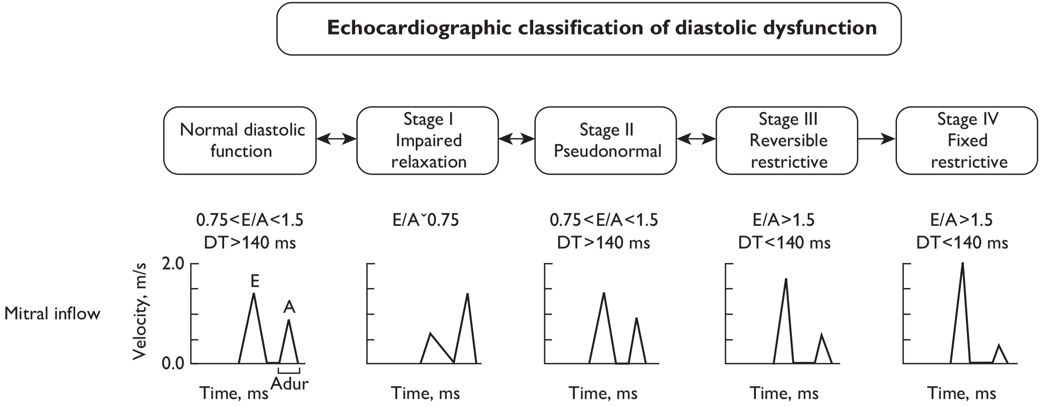
Echocardiographic classification of diastolic dysfunction
Normal diastolic function
Stage I Impaired relaxation
Stage II Pseudonormal
Stage III Reversible restrictive
Stage IV Fixed restrictive
0.75<E/A<1.5
DT>140 ms
E/Aˇ0.75
0.75<E/A<1.5
DT>140 ms
E/A>1.5
DT<140 ms
E/A>1.5
DT<140 ms
Mitral inflow
Velocity, m/s
2.0
0.0
E
A
Adur
Time, ms
Time, ms
Time, ms
Time, ms
Time, ms

Fig. 12.18 Echocardiographic classification of diastolic dysfunction.

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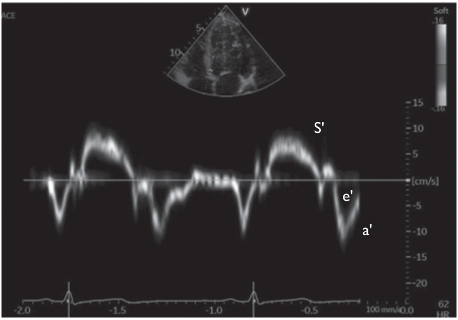
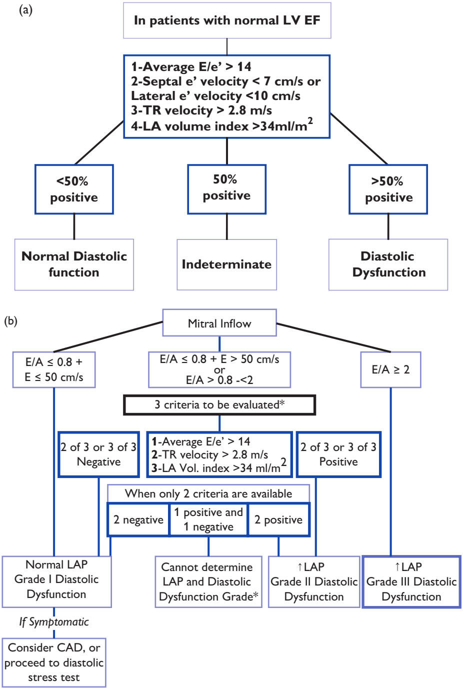

V
S'
e'
a'
15
10
5
[cm/s]
-5
-10
-15
-20
-2.0
-1.5
-1.0
-0.5
100 mm/s
0.0
62
HR

Fig. 12.19 Tissue Doppler imaging of the mitral valve annulus.

Image courtesy of Paulo Bulleros.


(a)
In patients with normal LV EF
1-Average E/e' > 14
2-Septal e' velocity < 7 cm/s or Lateral e' velocity <10 cm/s
3-TR velocity > 2.8 m/s
4-LA volume index >34ml/m2
<50% positive
50% positive
>50% positive
Normal Diastolic function
Indeterminate
Diastolic Dysfunction
(b)
Mitral Inflow
E/A ≤ 0.8 + E ≤ 50 cm/s
E/A ≤ 0.8 + E > 50 cm/s or E/A > 0.8 -<2
E/A ≥ 2
3 criteria to be evaluated*
2 of 3 or 3 of 3 Negative
1-Average E/e' > 14
2-TR velocity > 2.8 m/s
3-LA Vol. index >34 ml/m2
2 of 3 or 3 of 3 Positive
When only 2 criteria are available
2 negative
1 positive and 1 negative
2 positive
Normal LAP Grade I Diastolic Dysfunction
Cannot determine LAP and Diastolic Dysfunction Grade*
↑LAP Grade II Diastolic Dysfunction
↑LAP Grade III Diastolic Dysfunction
If Symptomatic
Consider CAD, or proceed to diastolic stress test

(* : LAP indeterminate if only 1 of 3 parameters available. Pulmonary vein S/D ratio <1 applicable to conclude elevated LAP in patients with depressed LV EF)

Fig. 12.20 Evaluation of left ventricular diastolic function. LAP, left atrial pressure; LVEF, left ventricular ejection fraction.

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TTE valvular evaluation: aortic pathology

- Echocardiography enables assessment of valve morphology and function, as well as the consequences of valvular pathology.
- It is essential in guiding medical and surgical management.

Aortic stenosis

- *Views:* aortic valve seen in PLAX, PSAX, 5Ch, and 3Ch views. Visual assessment of number of leaflets, best performed in PSAX (e.g. bicuspid/tricuspid/quadracuspid, mobility, and calcification—valve leaflet tips suggestive of rheumatic disease, global calcification suggestive of degenerative conditions).
- *Measurements:* LVOT diameter (PLAX) and PW Doppler (5Ch LV side of the valve, velocity time integral (VTI) traced from PW Doppler trace), CW of aortic valve (5Ch, maximum velocity at peak of velocity curve, VTI traced from velocity curves for continuity equation and mean velocity), planimetry of aortic valve (PSAX systole), and aortic dimensions (PLAX).
- The standalone Pedoff probe may be used to more accurately calculate peak velocities. For further information on classification and management of AS, see ➔ Aortic stenosis: overview, pp. 208–9.

Continuity equation

- This is based on the principle that the flow pre-valve is the same as that post-valve.
- LVOT flow = LVOT area × LVOT VTI by PW Doppler.
- LVOT area = π(maximum LVOT diameter in PLAX)^2
- AV flow = AVA × AV VTI by CW Doppler
- As LVOT flow = AV flow
- AVA = LVOT VTI/AV VTI × LVOT area

Aortic regurgitation

- *Views:* AR seen in PLAX, PSAX, 5Ch, and 3Ch views. Visual assessment of number of leaflets, mobility, and calcification.
- *Colour flow:* the colour flow width may give a qualitative assessment of severity and is defined as small, medium, or large, which corresponds to severity.
- *Measurements:* CW of aortic valve (pressure half-time calculated from peak to lowest point of the descending slope), VC (PLAX ideally), smallest flow diameter at aortic valve level in the LVOT, PISA (at Nyquist 40cm/s), aortic dimensions (PLAX), CW and PW of aorta to assess for diastolic flow reversal (suprasternal). Effective regurgitant orifice area (EROA) and residual volume are calculated by using PISA. For further information on classification and management of AR, see ➔ Aortic regurgitation: overview, pp. 214–15.

Proximal isovelocity surface area and vena contracta

- The regurgitant jet comprises a flow convergence zone and the vena contracta (VC) (see Fig. 12.21).
- The flow convergence zone is the zone of ↑ flow velocity in front of the regurgitant orifice. The size of this region relates to the size of the orifice and the degree of blood flow, and is measured by using the proximal isovelocity surface area (PISA) method by measuring the radius of the hemisphere in this area (see Fig. 12.22 and Colour plate).
- The VC is where the blood passes through the valve.
- The VC corresponds to the diameter of the regurgitant orifice.

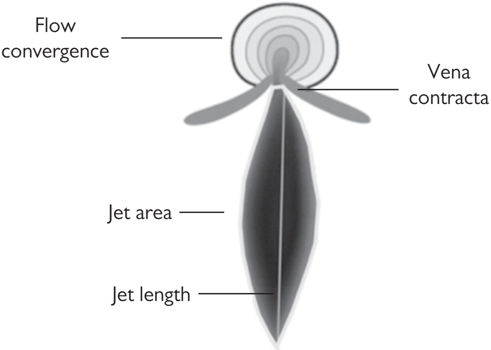

Fig. 12.21 Components of a regurgitant jet.

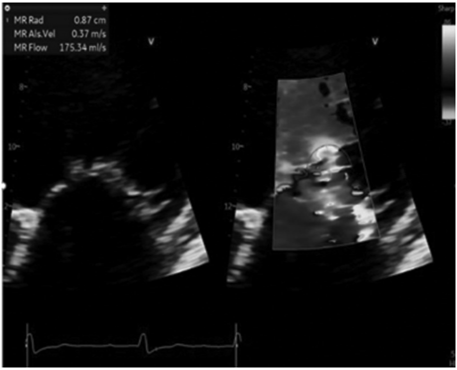
MR Rad 0.87 cm
MR Als.Vel 0.37 m/s
MR Flow 175.34 ml/s

Fig. 12.22 Measurement of PISA in mitral regurgitation. (See also Colour plate.)

Image courtesy of Paulo Bulleros.

TTE valvular evaluation: mitral pathology

- The MV comprises an anterior and a posterior leaflet.
- The anterior leaflet comprises scallops A1, A2, and A3, and the posterior leaflet comprises scallops P1, P2, and P3 (see Box 12.1).

Mitral stenosis

- *Views:* MS seen in PLAX, PSAX, 4Ch, 3Ch, 2Ch, and subcostal views. Visual assessment of number of leaflets, mobility, and calcification.
- *Measurements:* CW of MV (4Ch VTI traced from velocity curves, pressure half-time from the descending slope of the E wave), LA diameter and volumes (PLAX, 4Ch, 2Ch), CW of TR (calculation of PASP), planimetry of MV (PSAX mid diastole at the level of the valve leaflet tips).

For further information on classification and management of MS, see ➲ Mitral stenosis: overview, pp. 194–5.

Box 12.1 Mitral valve scallop views

- PLAX view: A2 and P2
- Four-chamber view: A3, A2, P1 (internal to external)
- Two-chamber view: P3, A2, P1 (left to right).

Mitral regurgitation

- *Views:* MR seen in PLAX, PSAX, 4Ch, 3Ch, 2Ch, and subcostal views. Visual assessment of number of leaflets, mobility, and calcification.
- *Colour flow:* the colour flow may give a qualitative assessment of severity. Commonly (but not always, e.g. in the case of eccentric jets/raised LA pressures), the greater the size and extent the colour jet extends into the LA suggests ↑ severity.
- *Measurements:* annulus (PLAX >35mm suggests dilatation).
- CW of MR (signal intensity is a qualitative guide to MR severity), PW at MV leaflet tips for MV inflow, VC (perpendicular to the commissural line), PISA (4Ch radius is measured in mid systole at a Nyquist limit of 40cm/s) (see Fig. 12.22 and Colour plate), pulmonary venous flow (4Ch), LA diameter and volumes (PLAX, 4Ch, 2Ch), CW TV (calculation of PASP).
- EROA and residual volume are calculated by using PISA.

For further information on classification and management of MR, see ➲ Mitral regurgitation: overview, pp. 200–1.

TTE valvular evaluation: pulmonary and tricuspid pathology

Tricuspid stenosis

- *Views:* TS seen in RV inflow, PSAX, 4Ch, and subcostal views.
- *Measurements:* CW of TV (VTI traced from velocity curves).

For further information on classification and management of TS, see ➔ Tricuspid stenosis, p. 220.

Tricuspid regurgitation

- *Views:* TR seen in RV inflow, PSAX, 4Ch, and subcostal views.
- *Colour flow:* may give a qualitative assessment of severity. Commonly (but not always, e.g. eccentric jets/↑ RA pressures), ↑ size/extent the colour jet extends into the RA suggests ↑ severity.
- *Measurements:* CW of TV (intensity is a qualitative severity guide), VC (4Ch), PISA (4Ch, PLAX, PSAX) measured in mid systole (Nyquist limit: 40cm/s). EROA and residual volume are calculated by using PISA.

For further information on classification and management of TR, see ➔ Tricuspid regurgitation, p. 221.

Pulmonary stenosis

- *Views:* PS seen in RV outflow, PSAX views.
- *Measurements:* CW of PV.

For further information on classification and management of PS, see ➔ Pulmonary stenosis, p. 222.

Pulmonary regurgitation

- *Views:* best seen in RV outflow, PSAX views.
- *Colour flow:* the colour flow guides assessment of severity by using the maximum colour jet diameter. Longer duration of flow and a wider jet as the jet crosses the PV are signs of severity.
- *Measurements:* jet diameter (measured in diastole immediately below PV); CW of PV (signal intensity is a qualitative guide to severity).

For further information on classification and management of PR, see ➔ Pulmonary regurgitation, p. 223.

TTE: strain imaging

- Strain imaging enables quantification of myocardial deformation.
- For a one-dimensional object, linear strain is defined as L–L0/L0 where L0 is the length at baseline and L is the measured length.
- The change in length is either positive (thickening) or negative (shortening), and is expressed as a percentage of the original length.
- Strain is therefore defined as the change in length normalized to the original length.
- Strain rate is the rate at which this occurs. This is expressed as S^{-1}.
- By using 2D echocardiography, deformation can be described as longitudinal, circumferential, radial, and rotational.
- Strain and strain rate imaging have been used to assess systolic and diastolic function of the LV and RV, and atrial function.

Doppler myocardial imaging

- This method of strain imaging utilizes TDI.
- TDI is used to measure velocities in two adjacent points and the distance between the points. Strain rate is the rate of change of the two velocities divided by the real-time distance between those points.
- *Advantages:* available, reproducible, good temporal resolution, direct strain rate calculation.
- *Disadvantages:* angle dependency, noise interference, requires high frame rates, influenced by global motion of the heart, interobserver variability.

Method

- Longitudinal strain and strain rate are measured from 2Ch, 3Ch, and 4Ch views.
- Radial strain and strain rate are measured from SAX views.
- Images should be taken parallel to the myocardial wall of interest.
- High frame rates are required (200 frames/s), which is achieved by reducing the sector width to the region of interest (ROI).
- Strain and strain rate analysis is performed offline.

Speckle tracking echocardiography

- The myocardium has characteristic speckling—these serve as natural markers which can be tracked from frame to frame.
- The change in position of the speckle enables calculation of its velocity and of strain and strain rate.
- *Advantages:* not angle-dependent, fewer artefacts, high reproducibility, and motion in any direction may be studied.
- *Disadvantages:* requires high image quality and high frame rates.

Method

- Frame rates of 60–110 frames/s are required.
- The 3Ch view is utilized to select the frame in which aortic valve closure occurs (end-systole).
- The 2Ch, 3Ch, and 4Ch views are required to assess regional and global longitudinal strain.
- SAX views are required for radial strain.

- Basal, mid, and apical cuts of the PSAX views are required for circumferential strain and rotation.
- Methods vary across vendors; however, usually require a tracing of the endocardium from each view to create an ROI. A second ROI is generated near the epicardium (see Fig. 12.23 and Colour plate). ROIs may be manually adjusted.
- *Time–strain curves:* enable calculation of regional and global peak and time to peak values.
- *Longitudinal strain:* analysis enables calculation of global and regional strain.
- *Radial strain:* represents radial deformation towards the centre of the LV and produces positive curves during systole.
- *Circumferential strain:* shortening of myocardial fibres at the LV perimeter in the SAX view, produces negative curves during systole.
- *LV twisting:* reciprocal rotation of the LV base and apex during systole. Calculated as the difference in mean rotation between the two.
- *LV torsion:* LV twisting divided by the distance between the base and the apex.

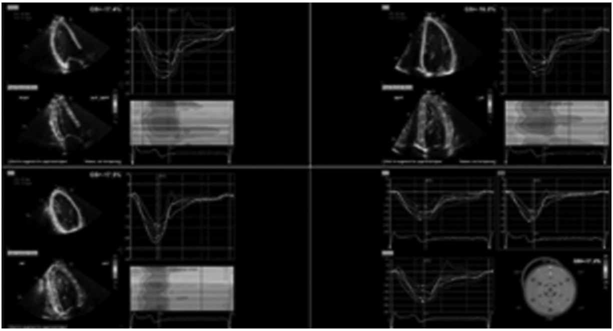

Fig. 12.23 Longitudinal strain measurement by using regions of interest. (See also Colour plate.)

Image courtesy of Paulo Bulleros.

Contrast echocardiography

- Contrast imaging relies on an echogenic agent to ↑ brightness within an image.
- Contrast agents contain gas bubbles of varying sizes. Right heart contrast agents contain larger bubbles than left heart contrast agents.

Right heart contrast agents

- *Example agent:* agitated saline.
- Short-lived, remain in venous circulation, absorbed by lungs.
- *Indications:* to identify a right-to-left intracardiac shunt (appearance of bubbles in the left heart within five cardiac cycles following right-sided opacification suggests a shunt), right-to-left intrapulmonary shunt (appearance of bubbles in the left heart within five cardiac cycles), improves Doppler signal of TV.
- Side effects of agitated saline are rare.

Left heart contrast agents

- *Example agent:* SonoVue©.
- Recommended dose is 2mL.
- Bubbles are small enough to cross the pulmonary circulation, and enter both venous and arterial circulation.
- *Indications:* to ↑ endocardial definition to assess LV function, to improve views during stress imaging, to improve detection of pathology such as thrombus and LV non-compaction, to improve Doppler signals.
- *Common side effects:* headache (2.1%), nausea (1.3%), chest pain (1.3%), reaction at injection site (0.6%). Allergic reactions are very rare (0.01%).

Persistent left superior vena cava

- May be identified by use of echo contrast agents
- Following injection of contrast into the left arm, contrast arrives in the coronary sinus prior to the right atrium

Dobutamine stress echocardiography

Indications

- Assessment of suspected CAD.
- Assessment of known CAD (to determine the risk of future events, assess viability/significance of lesions prior to revascularization, assess PCI and surgical results).
- Assessment of VHD (assessment of low-flow, low-gradient AS).

Contraindications

- NSTEMI (stress echocardiography may be performed 24–72h later).
- STEMI <4 days ago.
- Left main stem (LMS) disease that is likely to be significant.
- Symptomatic LV dysfunction.
- Previous life-threatening arrhythmias.
- Fixed LVOTO.
- Severe hypertension (>200mmHg).

Principles of stress testing

- Myocardial ischaemia is diagnosed by a reduction in blood flow on stress sufficient to reduce myocardial contraction.
- Two individuals should be present during the examination.
- Should have continuous monitoring, with ECG and BP recordings.
- A cannula is inserted into the arm.

Dobutamine

- Dobutamine infusion should be started at 5–10mcg/kg/min.
- At 3min interval, ↑ to 20, 30, and then 40mcg/kg/min.
- If the HR does not ↑, consider using atropine (0.3mg at 60s interval until HR response is seen).
- A 10% ↑ in HR signifies the end of the low-dose protocol.

Echocardiography

- Ideally, the frame rate should be >25 frames/s.
- Contrast may be required to improve the endocardial border definition.
- Baseline images taken from 4Ch, 2Ch, PLAX, and PSAX views.
- Following stress, images should be repeated at intermediate stage (70% of age-predicted HR), peak stress (>85% of age-predicted HR), and recovery.

Termination of the test

The test should be terminated if:

- Maximum dobutamine dose
- Achievement of target HR
- Severe chest pain
- ≥2 akinetic segments
- ≥2mm ST-segment depression/elevation
- >200mmHg SBP or >120mmHg DBP
- >40mmHg ↓ in BP
- Arrhythmias (SVT, AF, VT), frequent/polymorphic ventricular ectopics.

Assessment of images

- Compare rest and stress images by using the 17-segment model (see Fig. 12.17).
- Calculate the wall motion score: 1 = normal; 2 = hypokinetic; 3 = akinetic; 4 = dyskinetic; ↑ scores represent wall motion abnormalities.

Causes of akinesia

Scar—non viable

- Irreversible contractile function

Stunning—viable

- Improvement in contractile function throughout stress
- Stunned myocardium usually results from brief coronary occlusion, with improvement of contractile function over time

Hibernation—viable

- Improvement in contractile function at low-level stress. Function worsens again at higher levels of stress (biphasic response). This does not usually improve spontaneously but may improve following revascularization

Transoesophageal echocardiography

Transoesophageal vs transthoracic echocardiography

TOE is performed from within the oesophagus and gastric fundus, and has several advantages over TTE.

- *Resolution:* the TOE transducer is closer to the heart and great vessels, and has a higher frequency (5MHz vs 2.5MHz), thus providing ↑ resolution than TTE.
- *Unobstructed views:* the oesophageal approach affords an unobstructed view in those patients with poor TTE windows. TOE can be used in the intraoperative setting without interfering with the operative field.

Patient preparation

- The procedure is performed using local anaesthesia and, if required, IV sedation. Opting for local anaesthesia alone has the benefit of a more rapid recovery post-procedure, whereas sedation improves patient tolerance but ↑ the risk of side effects (e.g. cardiorespiratory depression).

Prior to procedure

- The patient is fasted for 4h.
- Any dentures are removed, and the back of the throat is sprayed with a local anaesthetic. IV midazolam (1–5mg) may be given for sedation.
- Some patients (e.g. paediatric or adolescent patients with complex CHD) will require general anaesthesia.
- IV flumazenil should be available to reverse the midazolam effect.

Procedure

- Oxygen and wall suction should be available.
- A nurse should be available to assist in monitoring of oxygen saturation, ECG, and BP during and after the procedure.
- The patient is placed in the left lateral position, with the neck flexed, and provided with a bite guard.
- It is the responsibility of the operator to ensure that the TOE probe has been thoroughly decontaminated prior to use. The sheathed probe is lubricated with gel and introduced gently to the pharynx. Once the patient swallows, the probe is advanced into the oesophagus. The patient should be told that the initial gag feeling will ease with passage of the probe from the pharynx into the oesophagus. Undue force must be avoided.
- TOE is performed with specialized transducers. The tips are flexible and operated by controls on the handle, which allows anterior, posterior, and lateral flexion.

Post-procedure

- The patient should be 'nil by mouth' for 1h post-procedure, for the effect of the local anaesthetic to wear off.
- The TOE probe should be thoroughly inspected for damage and disinfected following use. This should always be documented.

Pitfalls

- Serious complications are rare (<1%) and include oesophageal rupture, laryngospasm, gastric perforation, ventricular arrhythmia, and severe

hypoxia. Mortality rate is 1/10,000. Other complications include minor bleeding, sore throat/abrasions, and trauma to the teeth.
- The proximal aortic arch and upper portion of the ascending aorta is a 'blind spot' because of interposition of the trachea and right bronchus between the heart and oesophagus, and dissection could be missed.
- Due to the resolution of TOE, certain normal structures (e.g. Chiari network, aortic valve strands, prosthetic valve sutures) might be inadvertently mistaken as pathology.

Indications for transoesophageal echocardiography

- *Valve disease:* pre-surgical evaluation of aortic and mitral valves and/or assessment of prosthetic valves
- Infective endocarditis
- Cardiac source of embolism
- Prior to DC cardioversion (if patient has been insufficiently anticoagulated)
- Cardiac masses
- Congenital heart defects and intracardiac shunts
- Intraoperative monitoring
- ICU monitoring
- *Guiding interventional procedures:* atrial septal defect/patent foramen ovale closure, mitral valve valvuloplasty, trans-septal puncture, lead placement, cardiothoracic surgery, transcatheter aortic valve implantation
- Poor transthoracic echocardiography windows
- *Aortic pathology:* aortic dissection, aortic rupture, aortic aneurysm, atheroma

Contraindications to transoesophageal echocardiography

Absolute

- Oesophageal stricture
- Oesophageal tumour
- Oesophageal diverticulae

Relative

- Oesophageal reflux resistant to therapy
- Hiatus hernia
- Oesophageal/gastric surgery or bleed
- Oesophageal varices (transgastric views not advised and no bleed <4 weeks ago)
- Severe cervical arthritis
- Recent head and neck radiation

TOE: standard views

Probe movements

- *Advance/retract:* the probe can be moved forward to backward. Distance is demarcated on the probe in centimetres and corresponds to the distance from the patient's incisors to the probe tip.
- *Rotation:* can be rotated clockwise and anticlockwise manually.
- *The sector angle:* the angle of the imaging plane which is controlled by two buttons side by side on the control panel.
- *Ante-/retroflexion:* controlled by the large wheel on the control panel.
- *Lateral flexion:* controlled by the small wheel on the control panel.
- *Sector angle:* 0° is the transverse plane, which is orthogonal to the probe; 90° provides the longitudinal view.

Screenwiper principle

- The sector angle is taken from 0° to 135° in steps and then back again.
- 2D images, colour flow Doppler, and, if needed, CW/PW Doppler are taken (see Fig. 12.24).

Oesophageal views

Four-chamber view

(See Fig. 12.25A)

- *Position:* advance the probe to around 35cm from teeth at 0° angulation. Turn the probe to view all four chambers; this view is usually foreshortened.
- *Assess:* LV, RV, MV, TV. Measure RV and LV size, as well as MV Doppler measurements.

Five-chamber view

(See Fig. 12.25B)

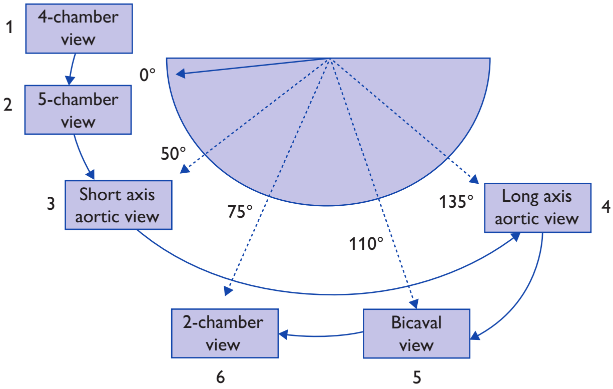

Fig. 12.24 Screenwiper principle.

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- *Position:* slight withdrawal of the probe provides the 5Ch view.
- *Assess:* LVOTO and AR.

SAX (AV) view

(See Fig. 12.25C)

- *Position:* from the 5Ch view, rotate to 50°.
- *Assess:* AV, TV, PV, IAS, coronary artery origins, and aortic root. Measure LA diameter, AV orifice, and aortic root diameter.

SAX (RV) view

(See Fig. 12.25D)

- *Position:* from the SAX (AV) view, rotate to 70–80°.
- *Assess:* PV, TV, RV, and RVOT. Measure RV and RVOT.

Long axis (LAX) (AV) view

(See Fig. 12.25E)

- *Position:* from the LAX, rotate to 135°.
- *Assess:* AV, MV, LVOT, AA. Measure aortic root, sinuses, ascending aorta, and LA size.

LAX (MV) view

- *Position:* from the LAX (AV) view, the probe is advanced slightly.
- *Assess:* MV, LV, and Doppler measures of MS/MR.

Atrial septum (bicaval) view

(See Fig. 12.25F)

- *Position:* from the LAX view, rotate to 110°.
- *Assess:* drainage of the SVC/IVC, assessment of the IAS, pulmonary venous drainage (right upper pulmonary vein), and measure TR.

Two-chamber (atrial appendage) view

(See Fig. 12.25G)

- *Position:* from the bicaval view, rotate to 75°.
- *Assess:* LV, MV, LAA, and pulmonary venous drainage (left upper pulmonary vein). Measure LV, EF, and MV.

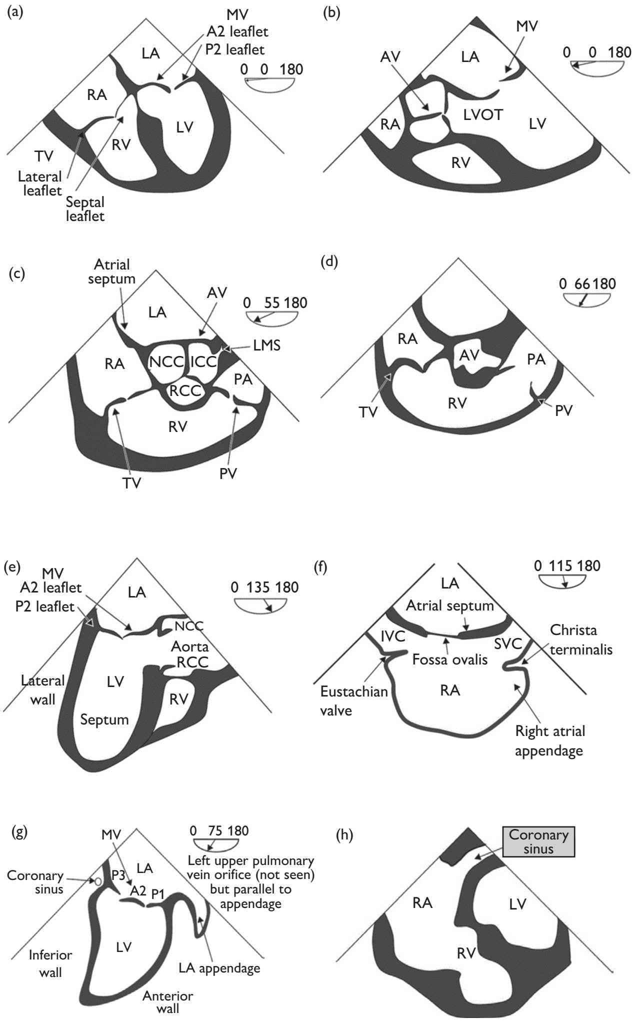
Pulmonary vein views

- *Right upper pulmonary vein:* seen best starting from the 4Ch view. The probe should be rotated to focus on the right side of the image and then withdrawn slightly.
- *Right lower pulmonary vein:* seen best starting from the 4Ch view. The probe should be rotated to focus on the right side of the image and then advanced slightly.
- *Left upper pulmonary vein:* seen best from the 4Ch view. The probe should be rotated to focus on the left side of the image and then withdrawn slightly.
- *Left lower pulmonary vein:* seen best from the 4Ch view. The probe should be rotated to focus on the left side of the image and then advanced slightly.
- Pulmonary vein flow should be measured in these views.

Coronary sinus view

(See Fig. 12.25H)

- The coronary sinus is seen best starting from the 4Ch view. The probe is advanced, so that the image shows a cut below the MV plane.


(a)
MV
A2 leaflet
P2 leaflet
0 0 180
LA
RA
LV
RV
TV
Lateral leaflet
Septal leaflet
(b)
MV
0 0 180
AV
LA
RA
LVOT
LV
RV
(c)
Atrial septum
AV
0 55 180
LA
LMS
RA
NCC
ICC
RCC
PA
RV
TV
PV
(d)
0 66 180
RA
AV
PA
RV
TV
PV
(e)
MV
A2 leaflet
P2 leaflet
LA
0 135 180
NCC
Aorta
RCC
Lateral wall
LV
RV
Septum
(f)
0 115 180
LA
Atrial septum
IVC
SVC
Christa terminalis
Fossa ovalis
Eustachian valve
RA
Right atrial appendage
(g)
MV
0 75 180
Left upper pulmonary vein orifice (not seen) but parallel to appendage
Coronary sinus
P3
LA
A2
P1
Inferior wall
LV
LA appendage
Anterior wall
(h)
Coronary sinus
RA
LV
RV

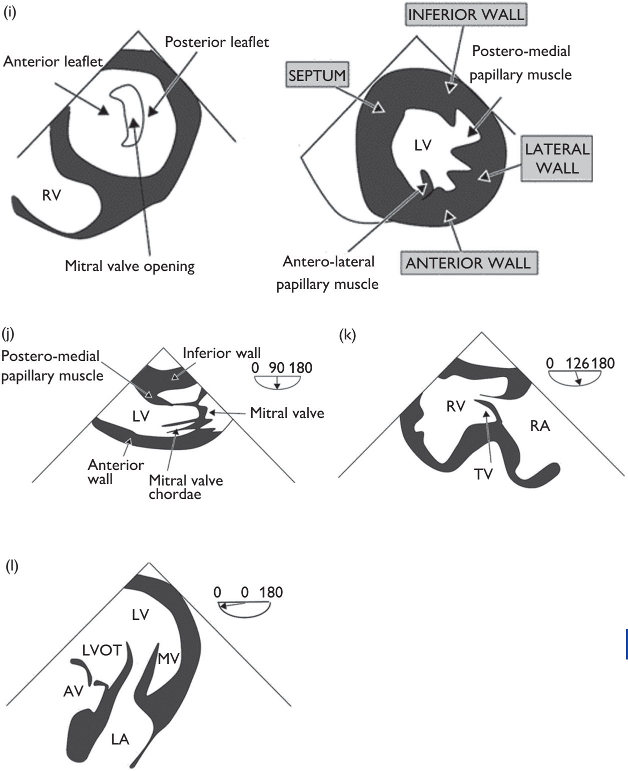

(i)
Anterior leaflet
Posterior leaflet
RV
Mitral valve opening
INFERIOR WALL
SEPTUM
Postero-medial papillary muscle
LV
LATERAL WALL
Antero-lateral papillary muscle
ANTERIOR WALL
(j)
Postero-medial papillary muscle
Inferior wall
0 90 180
LV
Mitral valve
Anterior wall
Mitral valve chordae
(k)
0 126 180
RV
RA
TV
(l)
0 0 180
LV
LVOT
MV
AV
LA

Fig. 12.25 (A–L) Standard transoesophageal echocardiography views. LCC, left coronary cusp; NCC, non-coronary cusp; RCC, right coronary cusp.

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Pulmonary artery views

- *Position:* from the SAX (AV) view, rotate to 40° and withdraw the probe until a SAX view of the aorta is seen.
- *Assess:* measure ascending aorta and PA.

Aortic views

- *Ascending aorta:* seen best from the PA view. As the probe is withdrawn, the ascending aorta is sequentially scanned.
- *Descending aorta:* from the 4Ch view, the probe is turned to face posteriorly. As the probe is withdrawn, the aorta is sequentially scanned.
- *Assess:* aortic pathology, including dissection, dilatation, atheroma, and thrombus. Measure aortic size and flow.

Transgastric views

SAX views

(See Fig. 12.25I)

- *Position:* from the 4Ch view, the probe is advanced by several centimetres. The probe is angulated forward to a right angle and then pressed up against the upper stomach wall.
- As the probe is moved forwards and backwards along the bottom of the heart, it is possible to see several levels of the LV in the SAX view.
- *Assess:* LV, MV, RV. Measure LV size and wall thickness.

LAX view

(See Fig. 12.25J)

- *Position:* from the SAX view, rotate to 90°.
- *Assess:* LV, MV. Measure LV size and wall thickness.

LAX (AV) view

- *Position:* from the LAX view, rotate to 110°.
- *Assess:* AV. Measure the aortic and LVOT velocities.

RV view

(See Fig. 12.25K)

- *Position:* from the LAX view, the probe is rotated clockwise.
- *Assess:* TV.

Deep transgastric view

(See Fig. 12.25L)

- *Position:* from the LAX view, the probe is advanced further into the stomach and the sector angle is reduced to 0°.
- *Assess:* LV, LVOT, and AV. Measure LV function, and aortic and LVOT velocities.

TOE: cardiac source of embolism

If a cardiac source of embolism is suspected, but not identified on TTE, TOE should be performed to examine the following.

Key features to look for

- LA clot or spontaneous contrast.
- LAA for clot.
- PFO.
- Atrial septal aneurysm.
- Atrial myxoma.
- LV cavity for LV thrombus (including apex).
- Aortic atheroma (>4–5mm; mobile and ulcerated aortic plaques have the highest risk of embolization) in the ascending arch and descending aorta.
- Aortic valve/MV for vegetations.

Diagnosis of intracardiac shunt

- A total of 10mL of saline is agitated by injecting between two syringes connected by a three-way tap. Some operators report better opacification with colloid (e.g. Haemaccel®) rather than with saline.
- Position the TOE probe for optimal visualization of the RA.
- Inject agitated saline.
- Repeat with Valsalva manoeuvre induced by asking the patient to cough or try to blow out the plunger from a 2mL syringe.
- The presence of bubbles in the left heart chambers within five cardiac cycles after opacification of the RA is required for a diagnosis.

TOE: valvular pathology

Transoesophageal echocardiography in mitral regurgitation

Key features to look for

Morphological assessment of the MV to determine the mechanism of regurgitation. Key views are shown in Fig. 12.26. Examine:

- Elongation or rupture of chordae
- Retraction of the chordae
- Prolapse or restriction of leaflets
- The subvalvular apparatus
- Annular diameter and degree of calcification
- LV size and regional wall abnormalities.

Classical mitral valve prolapse

- ≥2mm displacement of the MV tips beyond the mitral annular plane in the 3Ch view. This should not be confused with leaflet billowing—the presence of leaflet body motion behind the annular plane, with the MV tips remaining at/in front of the annulus.
- MV thickness >5mm.

Non-classical mitral valve prolapse

- The prolapsing leaflets are not thickened (<5mm) and are unaffected by myxomatous degeneration.

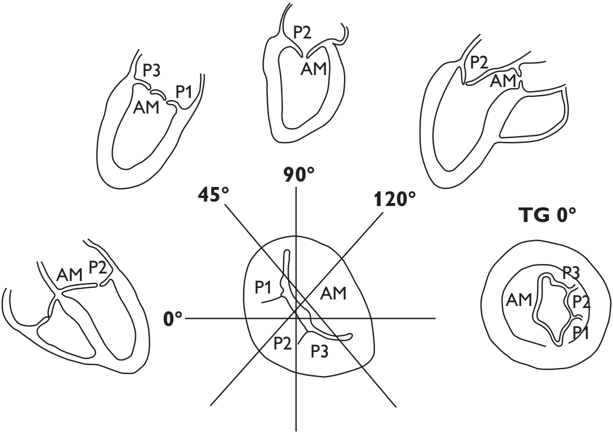

Fig. 12.26 Assessment of the mitral valve by transoesophageal echocardiography.
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Transoesophageal echocardiography in functional mitral regurgitation

- Typically, the MV is structurally normal, and therefore, MR is termed 'functional'.

Key features to look for

- Remodelling of the LV displaces the papillary muscle towards the apex; traction on the mitral leaflets causes incomplete leaflet closure.
- The zone of coaptation is displaced towards the apex, and 'systolic tenting' of the MV is seen.
- In the presence of an inferior or a posterior infarct, the posterobasal wall (site of the posteromedial papillary) of the LV may become aneurysmal. This can exert asymmetrical traction on the chordae, resulting in retraction of the posterior leaflet. There is abnormal apposition, and an eccentric, anteriorly directed jet of MR results.

Transoesophageal echocardiography for mitral valve repair

- Mapping of the prolapsing MV segments can be performed to aid in surgical planning.

Key features to look for

- Severity.
- Central/eccentric jet.
- If prolapse, which scallops are affected.
- Ruptured chordae and flail MV leaflets should be noted.
- The mitral annulus diameter is also measured (upper limit of normal is 35mm) to help guide selection of annuloplasty ring.
- Presence of annular calcification noted.

Transoesophageal echocardiography in mitral stenosis

- Assessment for suitability for percutaneous balloon mitral valvuloplasty.

Key mitral valve anatomy features to assess

- Mobility.
- Thickening.
- Calcification.
- Subvalvular thickening.

Transoesophageal echocardiography for aortic valve replacement

Key features to look for

- Cusp morphology and function.
- Aortic root, sinotubular junction, and annulus size.
- Ascending and descending aortic size (flow velocity in the latter).
- LVOT assessment (check for subaortic stenosis).
- Coronary ostia assessment.
- LV size and function.

Transoesophageal echocardiography for transcatheter aortic valve implantation

Key features to look for

- Cusp morphology and function.
- Planimetry of the aortic valve.
- Note calcification.
- Size and shape of the aortic sinus and sinotubular junction.
- Aortic annulus size.
- Coronary ostia size and height from the annulus.
- LV size and function.

TOE: valve prostheses

- TOE is especially sensitive in detecting MR in association with a prosthetic valve, because the LA is imaged in the foreground and is therefore devoid of artefacts generated by the metal elements of the prosthetic valve.

Paraprosthetic mitral leak

- *Sewing ring:* the mechanical prosthetic valve sewing ring appears as a bright ring attached to the mitral annulus.
- *Rocking valve:* if a significant circumference of the sewing ring has come away (e.g. from endocarditis), a rocking movement of the valve will be evident—this 'rocking prosthetic valve' is characteristic of partial dehiscence of the valve.
- *Valve mechanism:* the motion of the valve (e.g. tilting disc) should be assessed to ensure the discs/occluder are moving freely.
- *Paraprosthetic leaks:* flow outside the sewing ring is not normal, although small or mild jets may be seen early after valve implantation. This represents failure of the sutures attaching the valve ring to the annulus, either from technical failure or due to endocarditis.
- *Calcified annulus:* paraprosthetic leaks are more likely in the presence of a calcified mitral annulus.

Transprosthetic mitral leak

- Mechanical prosthetic valves have regurgitation during closure of the valve, which arises within the sewing ring (i.e. intraprosthetic).
- These 'closing jets' are a normal feature.
- In general, they are short jets, <3cm in length, with a narrow base <5mm and early systolic, rather than pansystolic, leak.
- Causes for abnormal intraprosthetic leak include pannus or thrombus preventing the occluder from functioning properly.

Tissue mitral prosthesis

- This should be assessed in the same way as for a mechanical prosthesis. The prosthetic valve leaflet should be assessed for:
    - Prolapsing leaflet
    - Flail leaflet
    - Thickened cusps (>3mm—higher risk of dysfunction).
- The Doppler signal for a flail cusp shows a characteristic striated 'zebra-stripe pattern'.

Obstruction of prosthetic mitral valve

This may be due to thrombus or pannus formation. The diagnosis is made by finding:

- Limited movement of the occluder or disc
- Haemodynamic confirmation by finding a high peak pressure gradient across the MV (>2.5m/s) or a prolonged pressure half-time (half-time >200ms).

Aortic valve prosthesis

- The orientation of the aortic valve means that the sewing ring will obstruct the view of the orifice of the valve for mechanical and stented tissue aortic valves. Thus, assessment of aortic paraprosthetic leak on 2D imaging is limited, compared with MV assessment.
- CW interrogation is not possible because the LVOT is orientated perpendicular to the US beam, when the aortic valve is assessed from the standard mid-oesophageal views.
- A combined TTE and TOE approach is required, because TTE is ideally suited to Doppler interrogation of the aortic valve.

Key features to look for on deep transgastric views

- Movement of the aortic prosthetic valve mechanism.
- Colour flow Doppler interrogation for AR.
- CW assessment of the aortic valve.
- CW measurement of the aortic valve gradient (expect mean gradient of <15mmHg).
- Regurgitation is most commonly transprosthetic in aortic tissue valves.
- The following may be visible on TOE: cusp thickening (>3mm predicts a risk of valve failure), cusp tear, cusp prolapse, and flail cusp.
- Rocking of the aortic prosthesis is due to dehiscence of the valve (40% circumference affected).

TOE: assessment of cardiac masses

Key features to look for

- *Myxomas:* the most common primary cardiac tumour, and specific features can be delineated on TOE (see Box 12.2).
- *Fibroelastomas:* benign tumours that attach to the valve apparatus. They have a frond-like appearance and may mimic vegetations or myxoma.
- *Malignant tumours:* primary cardiac and secondary metastatic disease can infiltrate the epicardium, myocardium, or endocardium, or present as an intracavity mass.
- *Pericardium:* pericardial involvement in malignant disease frequently causes pericardial effusion.
- Assessment of cardiac masses frequently requires multimodality imaging with CT/MRI ± biopsy in order to reach a definitive diagnosis.

Box 12.2 Features of a myxoma

- Attached by a stalk to the interatrial septum near the fossa ovalis in 90% of cases
- 75% are in the LA
- May have a speckled, cystic appearance with frond-like projections
- May be multiple. If they occur elsewhere, they may be mistaken for thrombus (tend to be homogeneous in appearance) or other tumours
- May cause valve obstruction

Pitfalls

- Normal anatomy is often mistaken for pathology.
- These structures include: Chiari network, Eustachian valve, trabeculations in the LAA, ridge separating the left pulmonary vein and LAA.

Cardiac computed tomography: overview

- Advances in CT technology have ↑ spatial and temporal resolution of cardiac images. Moreover, there has been significant ↓ in radiation doses, which now stand at around 1–2mSv.
- Cardiac CT is now considered a non-invasive alternative to invasive coronary angiography in low-risk patients with stable CAD.
- Can assess VHD, aortic, and valvular assessment.

Features of CT scanner

- *Gantry*: contains the X- ray tube and detector array (see Fig. 12.27).
- *Rotation time:* the time it takes for the gantry to rotate around the patient (depending on the system, this ranges from 250 to 500ms).
- *Collimation:* detector row width; ↓ width, ↑ spatial resolution.
- *Detector width:* number of detector rows multiplied by row width. The minimum number of rows for cardiac CT is 64 (64-slice CT).

Image reconstruction

Prospective gating

- The X-ray output is triggered by the patient's ECG. X-rays are only emitted in part of the cardiac cycle used for image reconstruction.
- ↓ radiation exposure, is used for those with a regular cardiac rhythm.

Retrospective gating

- The patient's ECG is recorded at the same time as image acquisition, which occurs throughout the cardiac cycle.
- Images are subsequently reconstructed from a point of the cardiac cycle.
- This enables the best images to be selected. Images can also be reconstructed from different time points of the cardiac cycle and used to form dynamic data sets for assessment of cardiac function.

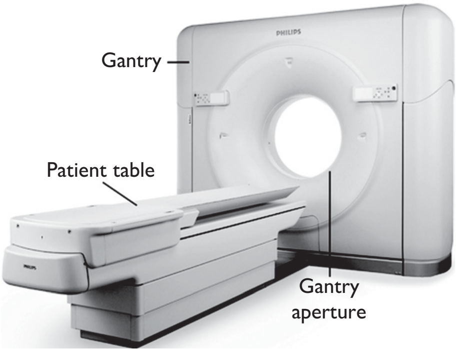

Fig. 12.27 CT scanner.

Image acquisition

There are three modes to enable data acquisition.

- *Spiral/helical acquisition:* with retrospective ECG-gated image reconstruction, the table is moved as the gantry rotates; the detectors create a spiral path around the patient; takes ↑ time, with ↑ radiation exposure. However, reconstructing images from any point in the cardiac cycle can avoid artefact and allows functional assessment.
- *Prospective ECG-triggered axial acquisition:* involves the patient remaining still. The X-ray output is triggered by the patient's ECG, and the patient is exposed to X-rays for a half of a rotation. The table is then moved by one detector width, and the next set of images are acquired. This is repeated until the desired scan length is obtained.
- *Prospective ECG triggered high pitch spiral acquisition:* a mixture of the above methods. Whilst the X-ray tube rotates, the table is moved rapidly, such that the whole length of the heart is covered in one heartbeat. Susceptible to artefact unless the HR is stable.

The four most important factors when acquiring an image

- *Gating:* should be synchronized with the patient's heartbeat.
- *High temporal resolution:* the gantry (containing the X-ray tube and detector array) must rotate quickly around the patient and effectively freeze the motion of the heart.
- *High special resolution:* the slices should be <1mm in width.
- *Coverage:* the entire heart should be covered with one breath-hold.

Image quality

This can be affected by artefacts and imaging speed.

Artefacts

- *Motion artefact:* this leads to blurring of the image.
- *Misalignment artefacts:* if there is an irregular heartbeat, the heart is not in the same position during each heartbeat. This creates 'steps' when the reconstructed image is combined from different cardiac cycles. Also occurs when the patient cannot adequately breath-hold.
- *High image noise:* this is caused by patients with high BMI.
- *Partial-volume effects/blooming artefacts:* calcification appears ↑ than in reality. Gives impression of ↑ stenosed coronary artery.

Imaging speed

- Temporal resolution ↑ with faster gantry rotation.

Image optimization

- *Patient:* the breath-hold technique and its importance should be carefully explained to the patient and practised.
- *HR and heart rhythm:* may be necessary to reschedule the appointment if the patient has multiple ectopics. In AF, CT may not be the most appropriate modality. ↓ HR is desirable for cardiac CT, can be achieved with β-blockers. Ideal HR is 60–65bpm.
- *Reconstruction:* in the case of motion artefacts, using a different cardiac phase may help to improve image quality. Depending on the HR, different phases of the cardiac cycle may give better images (e.g. ↓ HR—diastolic images, ↑ HR—later in systole).

Cardiac CT: coronary artery calcium scoring

- A CAC scan is performed by rapidly acquiring images using prospective ECG-triggered acquisition in diastole. The radiation dose is usually around 1.0mSv.
- The Agatston method is most commonly used to quantify coronary Ca^{2+}.
- Calcified atherosclerosis is an area of ≥3 adjacent pixels, with a density of >130 Hounsfield units.
- The CAC score may be useful in predicting future CV risk. Certainly, patients with a score of 0 have a very low risk of future CV events and may be reassured. However, long-term studies on CAC-guided improvement of outcomes are lacking.
- Therefore, the use of CAC scoring varies across guidelines and, at present, remains a Class IIb recommendation as a risk modifier in CV risk assessment in the ESC prevention guidelines.

Grades of calcified coronary atherosclerosis

- Normal: 0 Agatston units
- Mild: 1–99 Agatston units
- Moderate: 100–399 Agatston units
- Severe: ≥400 Agatston units

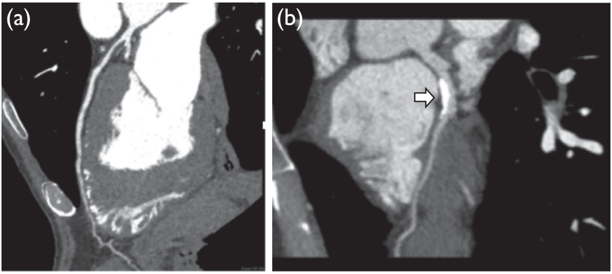

Fig. 12.28 (a) Normal vs (b) calcified left anterior descending artery.

Image courtesy of Dr Gemma Parry-Williams.

Cardiac CT: coronary angiography

- CTCA is a non-invasive test to rule in/out CAD in those with low/intermediate PTP. The radiation dose may be <1mSv in the most modern CT systems.
- Modern 64-slice and above CT scanners have been shown to provide excellent sensitivity (93–100%) and specificity (78–96%).

Image acquisition

- Iodinated contrast is injected into a peripheral vein. When contrast in the aorta reaches a specified level, images are acquired.
- CTCA is most commonly performed by using spiral acquisition or prospective ECG-triggered axial acquisition (see ➔ Image acquisition, p. 535). Images are acquired when the heart is motion-free, usually during mid diastole.
- β-blockers may be administered to ↑ duration of this phase. S/L nitrates should be given to further optimize the image.
- Images are analysed by using software, allowing manipulation in 2D and 3D reconstruction of the coronary arteries/cardiac chambers, known as 'volume rendering'.

Artefacts

- Coronary stents can cause significant artefacts. Blooming artefacts can expand the actual stent strut size. Beam hardening (where X-rays pass through high-density objects) can lead to hypoenhancement of the affected region. Heavy metals (e.g. titanium) cause ↑ artefacts. Smaller vessels are more affected than larger vessels.
- Stents manufactured without a metal backbone removes artefact.
- Clips and metal indicators at anastomotic sites can cause artefact.

Characterization of stenosis

- Stenosis is characterized as minimal (<25%), mild (25–49%), moderate (50–69%), severe (70–99%), and occluded (100%) (see Fig. 12.29).

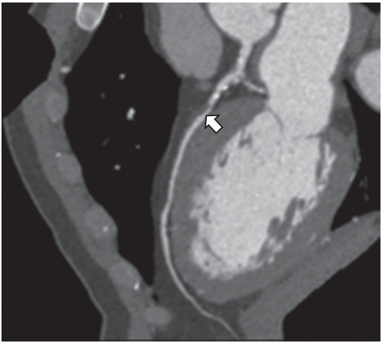

Fig. 12.29 Soft plaque in LAD.

Image courtesy of Dr Gemma Parry-Williams.

- Mild and below is unlikely to be flow-limiting, moderate possibly flow limiting, and severe probably flow-limiting. CT may overestimate disease severity in the presence of calcification.

Characterization of plaques

- CTCA enables differentiation between calcified and non-calcified plaques (see Figs 12.28b, 12.29).

Spotty calcification

- Divided into small (<1mm), intermediate (1–3mm), and large (>3mm) hyperdense plaques surrounded by non-calcified plaque. Strong correlation between spotty Ca^{2+} and vulnerable plaques.

Several features are associated with the potential for future rupture.

Low-attenuation plaque

- Plaques vulnerable to rupture are lipid-rich. Hounsfield unit measurement can differentiate between lipid-rich and fibrous plaques. ↓ attenuation values (<30 Hounsfield units) correlate with lipid-rich plaques.

Positive remodelling

- With coronary atheroma formation, the coronary artery enlarges at the lesion site. The remodelling index is the area of the vessel at the plaque site divided by the areas at the proximal and distal reference points. A value ≥1.1 suggests positive remodelling.

Napkin ring sign

- The napkin ring sign is a ring of high attenuation around a plaque and is strongly associated with future ACS events.

Cardiac CT: functional assessment of coronary lesions

- In general, CTCA overestimates coronary stenosis (cf. invasive angiography). Therefore, lesion functional significance is important.

CT functional flow reserve

- CT FFR is calculated by comparing the pressure within the coronary artery at rest and during simulated hyperaemia. Shown to correlate well with invasive FFR and may ↓ referral for invasive angiography.

Myocardial perfusion

- An emerging modality which assesses perfusion of the myocardium.
- Normally, distal blood flow ↑ via autoregulatory mechanisms in the presence of stenosis. In severe stenosis, these mechanisms can no longer compensate. Iodinated contrast taken up into the myocardium attenuate X-rays. In areas with ↓ perfusion, there is ↑ attenuation.
- May be performed at rest or under vasodilator-induced stress.
- As an imaging modality, there are still issues with optimization of images and ↓ radiation dose, and therefore, it is not widely utilized.

Other abnormalities

- Coronary artery anomalies can be well visualized, and the course tracked accurately.

Cardiac CT: valvular heart disease

Aortic valve

Valve stenosis severity

- CT is used as an adjunct to estimate aortic disease severity, particularly when this is not clear by using other modalities such as echocardiography and DSE.
- Higher calcification of the valve is suggested to predispose to a higher rate of progression. Has a role in those with asymptomatic severe AS to risk-stratify based on risk of progression.
- The proposed thresholds are >2065 Agatston units for men and >1274 Agatston units for women for severe AS.
- It can also provide information on concomitant aortopathy.

Transcatheter aortic valve implantation

- CT is the central imaging technique for planning of TAVI.
- Requires imaging of the whole aorta, iliac, and femoral arteries.
- Careful measurement of the aortic annular dimensions is required in order to choose the correct prosthesis size. If the prosthesis is too small, it may embolize and there may be paravalvular regurgitation. If the prosthesis is too large, there may be damage to the aorta.
- Other measurements that are also required include distance of the coronary ostia from the AV plane, aortic cusp, aortic sinus, sinotubular junction, and ascending aorta sizes. The risk of coronary occlusion is ↑ when the AV cusps are long, there are shallow sinuses of Valsalva, and a narrow sinotubular junction.
- Assessment of the iliac and femoral arteries provide information on vessel size, which ensures that the sheath does not exceed this size. Calcification and PAD can ↑ the risk of vascular complications.
- Assessment of the whole aorta provides information on contraindications to femoral access (e.g. dissection, thrombi, kinked aorta).

Mitral valve

Transcatheter mitral valve implantation

- This is a developing field and CT has the potential to become the central imaging technique for the selection of patients and planning of transcatheter procedures.
- The MV is a complex saddle-shaped structure, which cannot be fully elucidated in a single plane. Use of 3D techniques in CT may provide this valuable information.

Cardiac magnetic resonance imaging: overview

- CMR enables detailed assessment of cardiac anatomy and function.
- It provides high spatial and temporal resolution without the use of ionizing radiation.

MRI components and basic physics

- An MRI machine is composed of a magnet, three sets of magnetic field gradient coils, radiofrequency transmitter and receiver coils, a transmitter chain, a receiver chain, a data acquisition system, and a processing system and display (see Fig. 12.30).
- *Magnetic field:* created by coils carrying currents. The main magnetic field coil is within the outermost ring of the MRI scanner.
- *Gradient coils:* within the main magnetic field coil, there are three gradient coils which can vary the magnetic field. Therefore, the magnetic field may vary in different locations and can cause the protons within tissues to behave differently.
- *Proton alignment:* when a patient is placed within a strong static magnetic field, 1.5–3 Tesla in strength, this forces all protons in the patient to align with the field (see Fig. 12.31).
- *Radiofrequency coil:* the innermost coil. This is oriented at right angles to the main magnetic field and delivers a radiofrequency excitation pulse, causing magnetization of the protons to be flipped away from the longitudinal direction.
- *Receiver coils:* as the proton decays back towards the relaxed state, radiofrequency energy is emitted by the protons. Radiofrequency receiver coils cover the patient's thorax and receive signals.
- *T1 relaxation time:* longitudinal relaxation of a tissue.
- *T2 relaxation time:* time taken for transverse tissue relaxation.
- Relaxation times for recovery of longitudinal magnetization and decay of transverse magnetization are influenced by the local environment of the protons. The resulting signals are used to construct an image.
- Different sequences of pulses and varying magnetic field gradients can be used to emphasize different tissue characteristics or highlight particular anatomical details.

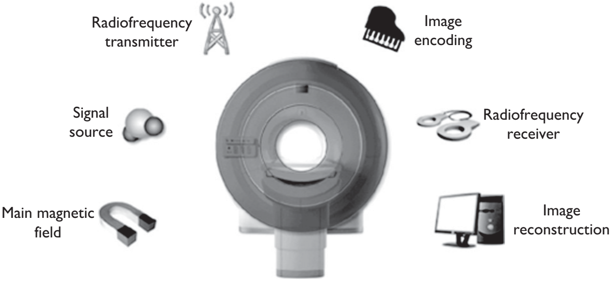

Fig. 12.30 Components of a magnetic resonance imaging scanner.

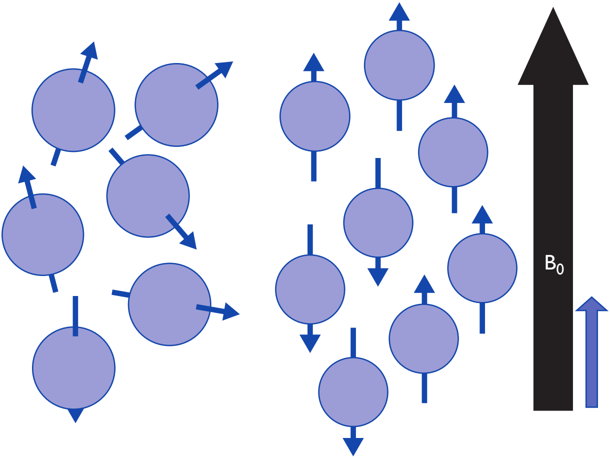

Fig. 12.31 Proton alignment. In the presence of an external magnetic field (B0), protons either align in a parallel or an antiparallel fashion to B0. As more protons align to B0, there is net magnetization in this direction.

CMR: T1 and T2 mapping

T1 mapping

- Tissue which has been excited by a radiofrequency pulse will return to its equilibrium state by a process known as relaxation.
- T1 (longitudinal) relaxation involves high-energy protons transitioning back to a low-energy state.
- Each tissue has its own T1 relaxation time. Changes in this time may suggest disease.

Native T1 mapping

- T1 maps are generated from a series of T1-weighted images where each pixel of the map has a specific T1 value.
- T1 maps can be displayed by using colour scales to highlight the differences between tissues (see Fig. 12.32 and Colour plate).
- Native T1 maps can be created without the need for a GBCA.

Post-contrast mapping

- T1 mapping can also be performed following administration of a GBCA. This shortens T1 times.
- T1 values at a prescribed time point post-GBCA may be influenced by native T1, the type and dose of contrast agent, the time to acquisition, body fat, eGFR, and haematocrit.
- It also falls down on estimation of ECV, and therefore, native T1 and ECV mapping are preferred.

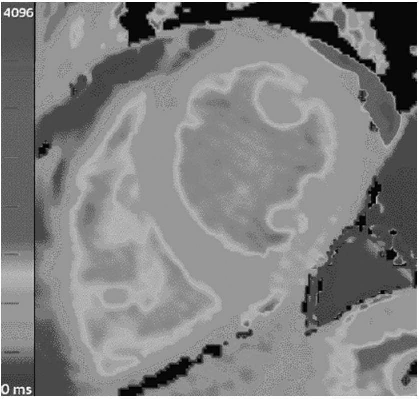

Fig. 12.32 An example of a good-quality native T1-map. (See also Colour plate.)

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ECV mapping

- ECV refers to the intravascular and interstitial myocardial components.
- This can be measured by using T1 mapping, GBCA, and haematocrit.
- The ECV of blood can be calculated as follows:
  - ECV blood = 100 − haematocrit (%)
- T1 is measured in the myocardium and blood before and after injection of a GBCA.
- Myocardial ECV is related to blood ECV as follows.
  - ECV = (1/T1 myocardium post-gadolinium − 1/T1 myocardium pre-gadolinium)/(1/T1 blood post-gadolinium − 1/T1 blood pre-gadolinium) × (100 − haematocrit)
- ECV is less dependent on the magnetic field strength compared with native T1 values. However, it can be affected by contrast entering other compartments and faster renal clearance than the exchange rate between compartments.
- In addition, like T1 mapping, ECV expansion is non-specific and may be due to oedema or infiltration. Ischaemia may also ↑ blood volume due to vasodilatation. This ↑ both ECV and T1 values.
- In the absence of confounding factors, ECV can act as an indicator for interstitial fibrosis.

Clinical utility

- ↑ T1 values may be seen in the acute setting such as in MI, myocarditis, and Takotsubo cardiomyopathy, as well as more chronically in infiltrative disease such as amyloidosis and cardiomyopathies and may be ↓ in Fabry disease.
- ECV is useful in identification of cases of diffuse myocardial fibrosis. ↑ ECV is associated with poorer outcomes and ↑ mortality.

T2 mapping

- T2 relaxation time is the time taken for transverse relaxation of a tissue.
- Each tissue has its own T2 relaxation time. Changes in this time may suggest disease.
- ↑ T2 values suggest an ↑ in water content of the tissue.

Clinical utility

- T2 mapping is useful for detection of oedema and inflammation, which may provide information on the area at risk in acute MI, diagnosis of myocarditis, and recognition of heart transplant rejection.
- It is important to note that T1 and T2 mapping still require further standardization and clear reference values.

CMR: safety

- Used with appropriate precautions, CMR is a very safe diagnostic technique.

Terminology

- *MR safe:* known to pose no hazard in all magnetic resonance (MR) environments.
- *MR conditional:* known to pose no hazard in a specific MR environment.
- *MR unsafe:* known to threaten or pose hazard in all MR environments.

Ferromagnetic implants

- The strong magnetic fields employed can convert any ferromagnetic implant into an object, with potentially lethal effects.
- All patients undergoing CMR examination should be screened for ferromagnetic implants, and equipment not specifically deemed *MR safe* should be excluded.

Absolute contraindications to cardiac magnetic resonance imaging

- ICD/PPM unless MR conditional
- Retained leads (particularly fractured)
- Metal foreign bodies in the eye/orbit
- Ferromagnetic cerebrovascular aneurysm clips
- Cochlear implants
- Insulin pumps

Implanted prostheses

- The precautions required depend on the material composition of the device and implant, and where doubt exists, the manufacturer should be consulted. Where no data exist to provide guidance, the risks and benefits of the scan must be carefully weighed.
- For weakly ferromagnetic devices, a major concern is device/implant dislodgement. It is generally recommended that scans are deferred for 6 weeks after implantation to allow the healing process to take place and to ensure the device is adequately anchored.
- Coronary and vascular stents are generally only very weakly ferromagnetic; studies can be performed safely in the majority of cases.
- The majority of heart valve prostheses and annuloplasty rings are *MR safe*. Others are *MR conditional*. The same applies to closure or occlusion devices, IVC filters, or embolization coils. Sternal wires and epicardial pacing leads are also safe.
- Implants may generate artefacts that hamper image interpretation.

Non-MR-compatible pacemakers/implantable cardioverter–defibrillators

- In addition to device migration, radiofrequency heating in leads can result in cardiac injury.
- Retained, particularly fractured, device leads pose a significant theoretical safety risk and are an absolute contraindication to CMR.

- The magnetohydrodynamic effects of the strong fields on the ECG can lead to inappropriate device behaviour, and direct effects on device programming/response can occur. MR-conditional PPMs and ICDs are now available. However, advice regarding the device and its programming should always be sought from local pacing departments prior to scanning.
- The need for a device should be carefully anticipated, and, if indicated, CMR undertaken before implantation, if possible, as up to 75% of such patients have, or will develop, an indication for CMR in their lifetime.
- ILRs have been safely scanned and most are MR conditional. They generate considerable artefact and, in theory, their performance can be influenced by strong magnetic fields. They should be interrogated before a scan is undertaken and again afterwards to clear the device buffers of any inappropriate artefactual data that may have accumulated during the scan.

Thermal injury

- Radiofrequency pulses can generate heating effects in wires or implants. Limb-to-limb skin contact can allow current loops to develop with thermal injury at the points of contact.
- Similar heating and burns can result from apparently benign objects such as standard ECG stickers. These must be removed from the patient prior to the scan, and monitoring carried out with carbon-based *MR-safe* stickers.

Injury to hearing

- Switching on and off of gradient fields can generate very loud noise (>100dB), which can lead to hearing loss. All patients and anyone present in the scanner room should wear protective headphones or earplugs.
- Rapid gradient switching can also cause unpleasant peripheral nerve stimulation.

Unstable patients

- Patients who are haemodynamically or otherwise unstable should not be taken into the scanner. There is limited scope for monitoring, and resuscitation equipment is not MR safe. Any patient requiring CPR must be transferred out of the scanner first.
- Together with limited access to the patient, these constraints make CMR an impractical modality for the unstable patient.

CMR: contrast agents

- GBCAs are predominantly extracellular contrast agents. These can help to identify scar/fibrosis.
- They may be cyclic or linear, and ionic vs non-ionic compounds.

Mechanism of action

- Following injection, GBCAs enter the intravascular and extracellular spaces and are eliminated renally. Normal myocardium allows swift wash in and washout of the contrast agent. However, accumulation occurs in scarred/fibrotic myocardium and leads to delayed washout.
- Acquisition of both early gadolinium-enhanced (EGE) and LGE images use T1-weighted pulse sequences with a 180° inversion recovery pulse sequence. The acquisition is timed (usually 10–20min after injection in a 1.5T scanner), so that magnetization of the myocardium crosses zero. At this point, the positively magnetized abnormal myocardium is bright (Fig. 12.33) and the normal myocardium appears black.
- EGE images are acquired 0–2min by using longer T1 values (450–600ms) following injection. The latter technique is useful to identify early oedematous myocardium following MI or a mural thrombus, which may appear dark.

Nephrogenic systemic fibrosis

- Although this is an extremely rare condition, it can be potentially life-threatening. This is thought to be triggered by the use of linear agents in those with severe renal impairment.
- It causes deposition of collagen in a combination of the heart, lung, liver, muscles, and skin.
- The safest agents to use include those with a cyclical structure (e.g. Gadovist®, Dotarem®, ProHance®). Intermediate safety agents include those with a linear, ionic structure (e.g. MultiHance®, Primosvist®,

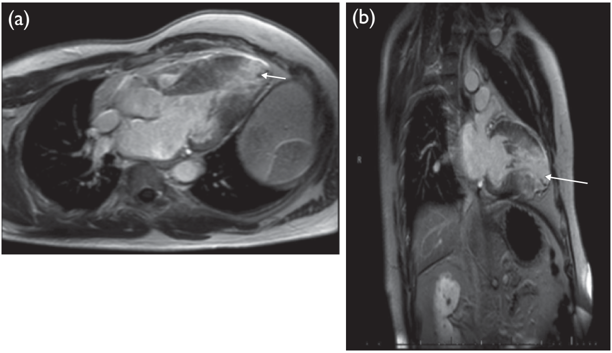

Fig. 12.33 Extensive late gadolinium enhancement seen in hypertrophic cardiomyopathy. (a) Four-chamber and (b) two-chamber views.

Courtesy of Dr Joyee Basu, St George's Hospital.

Vasovist®). The least safe agents include those with a linear, non-ionic structure (e.g. Magnevist®, Omniscan®, OptiMARK®).
- In individuals with eGFR of 30–60mL/min/1.73^2, the safest contrast agent should be used. Linear contrast agents are contraindicated where eGFR is <30mL/min/1.73^2.

Hypersensitivity

- Hypersensitivity reactions occur in between 0.004% and 0.7% of individuals. Anaphylactic reactions, however, are rare (0.001–0.01%).
- Risk factors for hypersensitivity reactions include a history of asthma and multiple food and drug allergies.
- Supportive care is usually sufficient. Cases of anaphylaxis require IM adrenaline, antihistamines, IV fluids, and steroids.

Contrast extravasation

- This is managed with limb elevation and application of ice packs.
- A surgical opinion should be sought if there is paraesthesiae, ↓ perfusion, or pain >4h.

Contrast deposition

- In 2015, the Food and Drug Administration (FDA) in the US issued a safety announcement regarding the deposition of GBCAs in the globus pallidus and dentate nuclei of individuals who had undergone multiple MRI scanning, some of whom also had normal renal function. However, the clinical relevance of these deposits is not known.

CMR: general considerations

- Assess for absolute contraindications (see ➔ Absolute contraindications to cardiac magnetic resonance imaging, p. 546).
- *Obese patients:* provide details of the patient's weight to assess whether the MRI table and scanner can safely accommodate the patient.
- *Possible language barriers:* ensure that an interpreter is present. Without patient cooperation, particularly with regard to breath-holding instructions, image quality may be significantly degraded.
- *Patient status:* ensure that the patient is able to lie flat for up to an hour and to breath-hold.
- *Orbital foreign bodies:* in those with suspected metallic foreign bodies in the eyes/orbits, arrange for orbital X-ray imaging before making the request if there is any doubt or the object has not been removed.
- *Caffeine:* patients undergoing adenosine stress perfusion studies should abstain from caffeine for 24h.
- β-*blockers/CCBs:* those receiving dobutamine should be advised to withhold these drugs for 48h.
- *Renal function:* a patient's renal function should always be checked.
- *Pregnancy status:* there is no documented harm from MRI in pregnancy. Nonetheless, adhering to the precautionary principle, it should be avoided, particularly in the first trimester, unless there is a compelling clinical indication and the scan cannot be deferred.
- *Breastfeeding*: limited gadolinium is passed into breast milk. Current ESC guidelines suggest it is appropriate to continue breastfeeding after CMR. However, some centres suggest women who are breastfeeding should be advised to express and discard breast milk for 24h after receiving gadolinium contrast media, as a precaution.

Major indications for cardiac magnetic resonance imaging

- Evaluation of ventricular function (gold standard)
- Assessment of ischaemia and myocardial viability
- Cardiomyopathy assessment
- Assessment of cardiac iron status
- Evaluation of congenital heart disease
- Evaluation of valvular heart disease
- Diagnosis and serial follow-up of aortic disease
- Assessment of pericardial disease and cardiac masses

CMR: coronary artery disease

- Stress perfusion and stress dobutamine CMR have sensitivities ranging from 83% to 91% and specificities ranging from 83% to 86% with regard to detection of coronary stenosis (>50%).
- Stress CMR has shown superiority over nuclear imaging and is now routinely used for assessment of ischaemia and viability.
- Lack of demonstrable ischaemia on CMR equates to event rates of 0.5–0.9%/year.

Ischaemia and viability assessment

- Myocardial ischaemia can be detected either by using GBCA enhanced first-pass perfusion imaging with vasodilator stress or by evaluation of wall motion under dobutamine stress, analogous to stress echocardiography.

Patient preparation

- *Caffeine:* use of adenosine to achieve vasodilator stress requires abstinence from caffeine-containing food and beverages (e.g. coffee, tea, chocolate, Coca-Cola®), ideally for 24h prior to testing.
- β*-blockers/CCBs:* 48h abstinence from β-blockers or rate-limiting CCBs is essential for dobutamine, but not vasodilator, stress-based protocols.

Principles of stress CMR

- *Dobutamine stress:* inotropic stimulation leads to ↑ oxygen demand. Downstream of a coronary stenosis, this is not matched by blood supply and ischaemia, and regional hypokinesia develop. Similar to TTE, each of the 17 LV segments are described as normokinetic, mildly hypokinetic, severely hypokinetic, akinetic, or dyskinetic. Ischaemia burden of ≥3/17 segments is considered high risk.
- *Adenosine stress:* at rest, microcirculation distal to the stenosed coronary artery is maximally dilated. Following administration of adenosine, vasodilatation of the microcirculation occurs distal to non-stenotic coronary arteries, but further dilatation downstream from the stenosed coronary artery is not possible. This lack of perfusion ↑ is detected by monitoring the first pass of contrast. If there is a haemodynamically significant lesion, then there will be ↓ signal.

Stress perfusion protocol

- Vasodilatation is achieved by infusing 140mcg/kg/min of adenosine until there is a haemodynamic response (typically 3min), followed by GBCA infusion and rapid acquisition of short-axis slices at basal, mid-ventricular, and apical levels, as the contrast enters the myocardium.
- The sequence requires a very long breath-hold, but satisfactory images can be obtained with very gentle breathing at the end of the longest breath-hold managed.

Contraindications

- Adenosine is contraindicated in the presence of high-grade AV conduction disease or severe asthma.
- Adenosine should not be co-administered with dipyridamole; the latter significantly ↑ adenosine half-life and can itself be used as a stress agent.

Limitations

- A limitation of MR perfusion imaging at 1.5T is the presence of dark rim artefact, which may lower the specificity for detecting subendocardial perfusion defects. Imaging at higher field strengths (3T) affords higher contrast-to-noise ratio and also reduces the risk of this artefact, further improving diagnostic specificity.
- Artefacts can often be identified by examining rest perfusion images, and interpretation can be further enhanced by examining LGE. The latter technique detects fibrosis and can further facilitate the differentiation of ischaemia from infarction.

Assessment of viability and hibernating myocardium

- *Viable myocardium:* defined as myocardium supplied by coronary arteries with flow-limiting CAD that exhibits contractile dysfunction in the absence of significant scar. This myocardium therefore has *potential* for contractile recovery following successful revascularization.
- *Hibernation:* defined retrospectively by the presence of evidence of functional recovery of the myocardium that was hypocontractile at rest following revascularization.
- Revascularization of patients without viable myocardium offers no apparent prognostic benefit.
- LGE CMR imaging allows identification of myocardial fibrosis. Viability is proportional to transmurality of fibrosis, with segments showing >50% fibrosis being defined as non-viable.

CMR in cardiomyopathy

Tissue characterization

- CMR facilitates accurate assessment of volumes, function, and myocardial mass, as well as tissue characterization.
- Reproducible; enables serial testing and assesses treatment response.

Dilated cardiomyopathy

- CMR can accurately quantify biventricular volume and function, permitting early detection of ventricular dilatation and dysfunction.
- LGE imaging discriminates between DCM and ischaemic pathology. Mid-wall fibrosis is typically detected in up to 28% of patients with DCM. Ischaemic scar occurs subendocardially.
- Mid-wall LGE identifies those at ↑ risk of arrhythmia and hospitalization.

For further information on DCM, see ➲ Dilated cardiomyopathy: overview, p. 232.

Myocarditis

- CMR can identify and quantify regional or global ventricular dysfunction resulting from myocarditis.
- Oedema, hyperaemia, capillary leak, and necrosis can be detected by using a combination of T2-weighted EGE and LGE.
- Lake Louise criteria for diagnosis of myocarditis requires two of:
  - Regional or global ↑ in signal intensity in T2-weighted images
  - ↑ global myocardial EGE on T1-weighted images
  - The presence of ≥1 focal lesions on LGE T1-weighted images.
- LV dysfunction and pericardial effusion are also suggestive.
- The criteria have a diagnostic accuracy of 78%.
- CMR should be repeated 1–2 weeks later if one criterion is met or if zero criterion is met, but there is strong clinical suspicion/recent symptom onset.

For further information on myocarditis, see ➲ Myocarditis, p. 284.

Hypertrophic cardiomyopathy

- LGE hyperenhancement of RV insertion points and marked LVH.
- LGE identifies those at ↑ risk of arrhythmias, HF, and SCD.

CMR vs echocardiography

- The multiplanar capabilities and high spatial resolution of CMR provide a number of advantages over echocardiography.
- CMR gives ↑ accurate quantification of LVH. TTE may under-/overestimate wall thickness. Underestimation typically occurs when LVH is confined to the apex, posterior septum, or anterolateral wall.
- At the basal anteroseptum, a common site for hypertrophy, CMR allows more accurate differentiation of the LV septum from RV–septomarginal trabeculation (often overestimated on TTE).
- CMR can identify apical trabeculation, differentiating apical HCM from LVNC/endomyocardial fibrosis; may appear similar on TTE.
- Although CMR identifies LVOTO and MV SAM, ↑ TTE temporal resolution is better for quantifying LVOTO at rest and on exertion.

For further information on HCM, see ➲ Hypertrophic cardiomyopathy: overview, p. 240.

Arrhythmogenic cardiomyopathy

- CMR is an important modality for diagnostic evaluation, given its ability to precisely and accurately image the RV, enabling identification of features fulfilling the ARVC Taskforce Criteria.
- It can identify fibrofatty infiltration (T2 imaging), scarring (LGE), thrombus, and inflammation.
- RV LGE is seen in up to 71%, and LV LGE in up to 25% of patients.

For further information on ACM, see ➔ Arrhythmogenic cardiomyopathy: overview, p. 250.

Left ventricular non-compaction

- Traditionally, diagnosed by TTE. However, the apex is poorly visualized with TTE. High spatial resolution of CMR facilitates diagnosis.
- The diagnosis is made if the ratio of non-compacted-to-compacted myocardium is >2.3:1 in diastole.
- CMR can detect LV thrombus, a major complication of LVNC.

For further information on LVNC, see ➔ Left ventricular non-compaction: overview, pp. 258–9.

Amyloidosis

- CMR demonstrates concentric LV myocardial thickening due to amyloid infiltration. Other features: thickening of the IAS, RA free wall, and valve leaflets; in the later stages, systolic dysfunction and consequences of diastolic HF.
- CMR can reveal circumferential subendocardial to mid-wall LGE in affected patients. LGE distribution is often in a non-coronary pattern, differentiating it from subendocardial MI.
- Cardiac amyloid also leads to ↑ native T1 times and ECV.

Sarcoid

- CMR may reveal patchy LGE. T2 images can show oedema, which can signify acute inflammation and may identify active disease.
- Use of CMR ↑ the likelihood of diagnosing cardiac involvement using the above clinical criteria, but the diagnosis remains challenging.

Iron overload

- May occur when iron processing is disrupted (e.g. haemochromotosis). Those with haemoglobinopathies (e.g. β-thalassaemia major) require repeated transfusions and may also develop iron overload.
- Cardiac iron correlates poorly with serum iron status markers and with biopsy-determined liver iron. Before CMR, there was no accurate way to predict chelation therapy intensity and initiation timing.

Protocol to measure iron overload

- *T2 relaxation time:* time taken for transverse relaxation of a tissue.
- A radiofrequency pulse is applied and deflects spinning protons from their state of equilibrium. The more iron present, the quicker the protons return to their original state. This parameter is T2* (T2-star).
- Can measure T2* in a single breath-hold and is highly reproducible.
- T2* values of <20ms suggest significant cardiac iron loading.
- This technique has been validated against iron content of biopsies.

CMR in valvular heart disease

- Echocardiography remains the modality of choice for evaluation of most VHD.
- However, CMR provides complementary information and is now the preferred investigation, where available, for pulmonary disease due to superior visualization to echocardiography.
- CMR provides multiple planes, enabling visualization of desired structures, even in patients with difficult echocardiographic windows.

Stenosis and regurgitation

- Phase-contrast flow velocity mapping can enable determination of peak flow velocities, estimation of valve gradients, and relatively accurate quantification of regurgitant fractions.
- Through-plane flow maps are used to characterize flow jets and facilitate accurate positioning for in-plane measurements of flow velocity.

Planimetry

- CMR can be used to planimeter the aortic valves (systole) and MV and TV (diastole), allowing direct estimation of the valve area.

Evaluation of the right heart

- CMR enables the pulmonary valve and RV to be imaged in exquisite detail and is invaluable for precise evaluation of PR, as well as PA anatomy, in patients with ToF and other CHD with significant RV involvement.

Evaluation of the aorta

- CMR provides additional anatomical information such as the dimensions of the aorta in a patient with bicuspid aortic valve disease or suspected CoA.
- It is particularly useful where serial, accurate, and reproducible measurements of aortic root dimensions are needed.

CMR in congenital heart disease

- The lack of ionizing radiation (a particular concern in adolescents or young adults), a wide field of view, and the versatile multiplanar imaging capability afforded by CMR make it the modality of choice for evaluation and follow-up of patients with CHD.
- The wide field of view allows assessment of visceroatrial *situs* and cardiac position. AV and VA concordance can also be evaluated.
- CMR is particularly useful in those with complex anatomy (e.g. Fontan circulation) or after repeated surgical repairs where scar tissue may give rise to poor echocardiographic windows.

Shunt calculations

- Accurate assessment of pulmonary and aortic flows allows shunt ratios (Qp/Qs) to be readily calculated.
- Assessment of the effects of lesions may be critical for determining the nature and timing of any surgical intervention.

Evaluation of coronary arteries

- The origin and proximal course of coronary arteries can be delineated with whole-heart coronary imaging sequences, allowing identification of anomalous coronary arteries and definition of their course with respect to the aorta and PAs.
- This can facilitate identification of malignant courses and planning for surgical repair.

Evaluation of the aorta

- CMR is particularly adept at imaging the aorta and other great vessels. PDA and associated anomalies are readily defined.
- Aortic coarctation can be comprehensively assessed, including lesion severity and suitability for percutaneous treatment, or evaluation of re-coarctation or aneurysm formation following surgical repair.

CMR for pericardial disease and cardiac masses

- CMR enables a detailed assessment of the pericardial anatomy and the presence of active inflammation, and assists in characterization of pericardial tumours and cysts.

Pericarditis and pericardial effusions

- *Inflammation:* a second-line investigation in acute pericarditis, CMR (T2 images) can show areas of ↑ pericardial signal, reflecting acute inflammation. Pericardial LGE is another sign of inflammation.
- *Pericardial thickening*: CMR can reveal pericardial thickening. A pericardium of ≥3mm is suggestive of pericarditis.
- *Pericardial effusion:* CMR is particularly sensitive and may detect effusions of ≥30mL. Although effusion assessment can be accomplished with TTE, CMR is helpful in loculated effusions, detecting pericardial haematoma, poor echocardiographic windows, and suspected neoplasia where information is required on surrounding tissues.
- *Effusion type*: transudates have ↑ T1 intensity and ↑ T2 intensity; exudates have ↓ T1 intensity and intermediate T2 intensity.
- CMR may identify myocardial involvement. In the late phase, CMR can diagnose pericardial constriction and assess for surgery.

Pericardial constriction

- The pericardium is thickened and often has ↓ signal due to fibrotic tissue and Ca^{2+}, which has poor water content.
- Other features may include bi-atrial dilatation, IVC and hepatic vein engorgement, pleural effusions, and RV cavity narrowing. RV long-axis function is often preserved (cf. RCM).
- Real-time free-breathing cine sequences can detect the haemodynamic effects of pericardial constriction. The RV normally starts to fill before the LV. Constriction prevents RV expansion, and the IVS is pushed from right to left in early diastole ('early septal bounce'). Inspiration, by ↑ RV filling, ↑ leftward septal movement in early diastole, particularly after the first heartbeat following inspiration. This is not seen in RCM.

Pericardial defects

- There may be partial or complete absence of the pericardium. Most commonly, the left side of the pericardium is involved. There is usually marked displacement of the heart, and interposition of a tongue of lung parenchyma between the aorta and the PA and between the inferior surface of the heart and the diaphragm.
- Partial defects may be complicated by cardiac herniation, particularly of the LAA, which can strangulate and infarct.

Pericardial cysts

- Congenital, usually unilocular, structures arising in the pericardium.
- Cysts have ↑ T2 signal due to their water content and ↓ T1 signal.
- Do not enhance with gadolinium as there is no direct blood supply.

Cardiac masses

- CMR can assess lesion location (i.e. intramural vs intracavity) and identify multiple (metastatic) deposits, as well as pleural and pericardial effusions, which ↑ the index of suspicion for malignant disease.
- CMR evaluation of any suspected cardiac mass involves standard CMR sequences, assessing the presence of contrast enhancement, and perfusion imaging, as well as LGE imaging.
- Tagging can be used to assess deformation with cardiac contraction and reveal their continuity or relationship with cardiac muscle.
- CMR also enables imaging of vascular structures and the surrounding anatomy, as part of planning a surgical approach.
- Cardiac mass/malignancy characteristics are shown in Table 12.2.
- Histological correlation is often required for further characterization.

Table 12.2 CMR characteristics of cardiac masses and malignancies

Mass	CMR characteristic
Thrombus	Hypointense T1/T2 No LGE
Myxoma	Iso-/hypointense T1 Hyperintense T2 Heterogeneous LGE
Fibroelastoma	Usually too small for further characterization
Fibroma	Hypointense T1/T2 LGE
Haemangioma	Heterogeneous/hyperintense T1/T2 Significant and prolonged LGE
Lipoma	Hyperintense T1/T2 reduced with fat suppression
Angiosarcoma	Heterogeneous T1/T2 Heterogeneous LGE 'sunray appearance'
Sarcoma	Isointense T1 Hyperintense T2 Heterogeneous/variable LGE
Rhabdomyoma	Isointense T1 Iso-/hyperintense T2 No/minimal LGE
Lymphoma	Isointense T1/T2 No/variable LGE
Metastasis	Hypointense T1 Hyperintense T2 Heterogeneous LGE

Source: data from Camm JA *et al*. *ESC Textbook of Cardiovascular Medicine* (2018).

Nuclear cardiology: overview

- Nuclear medicine investigations involve injection of a radiotracer (^{201}thallium (^{201}Tl) chloride or technetium-99m (^{99m}Tc)-bound molecules), which emit photons.
- These are taken up by the myocardium proportionally to blood flow to these areas.
- This distribution can be imaged by SPECT using an Anger gamma camera.

The Anger gamma camera

Crystal

- The key component of a gamma camera is a large flat, circular or rectangular sodium iodide crystal, activated by non-radioactive thallium—NaI(Tl). The crystal is a 'scintillator' (i.e. absorption of a gamma photon via the photoelectric effect yields a burst of photons of visible light within 1mm of the interaction).

Collimator

- The side of the crystal facing the patient is shielded by a collimator, a lead disc penetrated by thousands of uniform parallel channels separated by thin septa.
- Only photons travelling perpendicular to the collimator can penetrate the channels and enter the crystal, whereas the remainder are absorbed by the lead septa. Thus, gamma photons originating from a particular area of the heart can only enter a selected area of the NaI(Tl) crystal, maintaining spatial information.

Photomultiplier tubes

- The side of the crystal away from the patient is viewed by a hexagonal array of up to 100 photomultiplier tubes (PMTs). These convert the weak signal carried by photons of visible light leaving the crystal into a detectable electrical pulse.
- The pattern of activation of PMTs signals the location of the originating scintillation event, with the largest electrical pulse being generated in the PMT closest to the event.
- These electrical pulses are then digitized to create digital pixels of the final image array. The image is reconstructed to produce 3D images, demonstrating the distribution of the radiotracer.

Newer cameras

- Due to low resolution, exposure to radiation, and the need for bulky equipment, newer cameras have been developed.
- These contain cadmium–zinc–telluride crystals, which ↑ the sensitivity of the device (through higher attenuation of photons). The cameras allow conversion of light directly into electrical pulses. This, in turn, means that PMTs are not required. A higher spatial resolution is also attained when compared with conventional SPECT.

SPECT image acquisition and display

Planar acquisition

- Acquisition and summation of scintillations by the head of a gamma camera for a few minutes yield a planar scan, which represents the 3D distribution of a radiopharmaceutical agent within a patient as a 2D image.

SPECT acquisition

- SPECT imaging involves the acquisition of a series of planar projections at different angles, as the head(s) of the gamma camera orbit(s) the patient.
- A dual-headed camera is preferred, with the heads positioned at 90° to one another to halve acquisition time. A typical MPS acquisition might involve 64 projections (32 per head) acquired over a 180° orbit and taking 16min.
- Filtered back-projection or iterative reconstruction is used to produce a set of transaxial sections through the patient. The transaxial slices can then be reorientated to the axes of the heart to produce vertical long-axis, horizontal long-axis, and short-axis slices.
- The count density of each pixel within the reorientated slices is displayed relative to the pixel of maximal counts in the myocardium (0–100%), using a greyscale or colour spectrum. Stress slices are displayed above corresponding rest slices to facilitate comparison.

Gated SPECT

- SPECT acquisitions can be 'gated' to the ECG. The R–R interval is divided into eight or 16 frames, and each planar projection is acquired as eight or 16 corresponding images. Each frame is reconstructed and reorientated separately to produce SPECT slices that represent the LV at a particular point in the cardiac cycle. Static slices to assess perfusion can be obtained from the same acquisition, by summing the frames for each planar projection.
- Gated slices can be viewed in a looped cine format to assess regional function in terms of wall excursion and thickening. Commercially available software is used to fit endocardial and epicardial boundaries and to determine end-diastolic volume, end-systolic volume, and EF.

Attenuation correction

- Gamma photons emitted from the heart are variably attenuated by soft tissue. This can produce spurious apparent perfusion abnormalities in the processed slices (attenuation artefacts). Many modern gamma cameras allow attenuation correction (AC).
- A *transmission* acquisition is performed by using one or more scanning gadolinium sources or X-ray CT, and an attenuation map is reconstructed. This is used to correct the *emission* acquisition, which is acquired simultaneously (gadolinium approach) or separately (CT approach).

Myocardial perfusion scintigraphy

Indications

- Detection of CAD in those with an intermediate PTP.
- Patients who are unable to exercise.
- Patients with resting ECG abnormalities (e.g. LBBB).
- Guidance of management in known CAD:
  - Post-MI.
  - Post-coronary angiography.
  - Post-coronary revascularization.
- Assessment of myocardial viability, ischaemia, and function in ischaemic LV dysfunction.

Overview

- At rest, myocardial perfusion distal to a flow-limiting coronary stenosis usually remains normal due to progressive arteriolar dilatation.
- During cardiac stress, there is ↓ vasodilator reserve available, and perfusion will be lower than that downstream of an unobstructed vessel.
- A radiopharmaceutical perfusion tracer is injected during cardiac stress and taken up by cardiac myocytes proportionate to blood flow.
- Subsequent SPECT imaging is performed, and the distribution of radionuclide reflects myocardial viability and perfusion at the time of tracer injection (i.e. during stress).
- A separate imaging study is performed after injection of the tracer at rest or following redistribution of the stress injection, and the distribution of radionuclide primarily reflects viability.
- Sensitivity of 85–90% and specificity of 70–75% for CAD detection.
- A normal MPS scan does not rule out non-obstructive CAD.

Cardiac stress

- Dynamic exercise stress (treadmill or bicycle) is the most physiological form of stress.
- Many patients referred for MPS are unable to exercise to their target HR, and pharmacological methods are required. The drugs used fall into two categories:
  - Primary vasodilators (dipyridamole or adenosine): first choice, unless contraindicated by airways disease or AV block
  - Inotropic agents (dobutamine).
- *Adenosine:* causes direct coronary vasodilatation via A_{2a}-receptors.
- *Dipyridamole:* acts indirectly, ↑ endogenous adenosine by inhibiting its breakdown and reuptake.
- *Dobutamine:* a synthetic β-agonist, ↑ myocardial oxygen demand, causing secondary coronary vasodilatation.

Radiopharmaceutical perfusion tracers

- MPS perfusion tracers in routine clinical use are thallium-201 (^{201}Tl) and the newer technetium-99m (^{99m}Tc)-based tracers sestamibi and tetrofosmin.
- ^{201}Tl is a superior perfusion tracer physiologically, but the ^{99m}Tc agents have several practical advantages. The images produced are of higher quality because the photons are of ↑ energy and can be gated to assess LV function. In addition, the ↓ half-life (6h vs 73h) ↓ radiation exposure to the patient.

Thallium-201

- ^{201}Tl, given as thallous chloride, is a cyclotron-generated isotope.
- It enters myocytes down the electrochemical gradient, similar to K^+.
- Following injection at peak stress, it gradually equilibrates between the intracellular and intravascular compartments, and so immediate imaging is required.
- Redistribution imaging is after 4h, to assess perfusion at rest. For optimal viability assessment, ^{201}Tl may be reinjected at rest.

Technetium-99m-labelled tracers

- ^{99m}Tc is produced from a generator and is complexed with an organic molecule (sestamibi or tetrofosmin).
- ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin diffuse passively into myocytes where they bind to mitochondria.
- The absence of significant redistribution means that imaging can be performed conveniently 30–60min after injection, but separate injections are required during stress and at rest.
- A 2- or 1-day protocol may be used. A nitrate may be given prior to the resting injection, to maximize uptake.

Image findings

Perfusion defects

- *Fixed (on both stress and rest acquisitions):* suggests scar following MI.
- *Reversible (on stress acquisition only):* suggests inducible hypoperfusion of viable myocardium distal to flow-limiting coronary stenosis (see Figs 12.34 and 12.35 and Colour plate).
- *Viable myocardium:* may be identified on redistribution of the tracer from remote to viable myocardium a few hours after injection.
- Characterized by location (coronary territory), extent, and severity. Multiple affected coronary territories and perfusion defects in >10% of the myocardium is considered high risk. A normal stress perfusion study is associated with a cardiac event rate of 1%/year.
- May need to be distinguished from artefacts (e.g. anterior soft tissue attenuation in women, inferior attenuation in men).

Other high-risk findings

- ↑ lung uptake of ^{201}Tl, transient ischaemic dilatation (TID)—LV cavity larger post-stress than at rest.

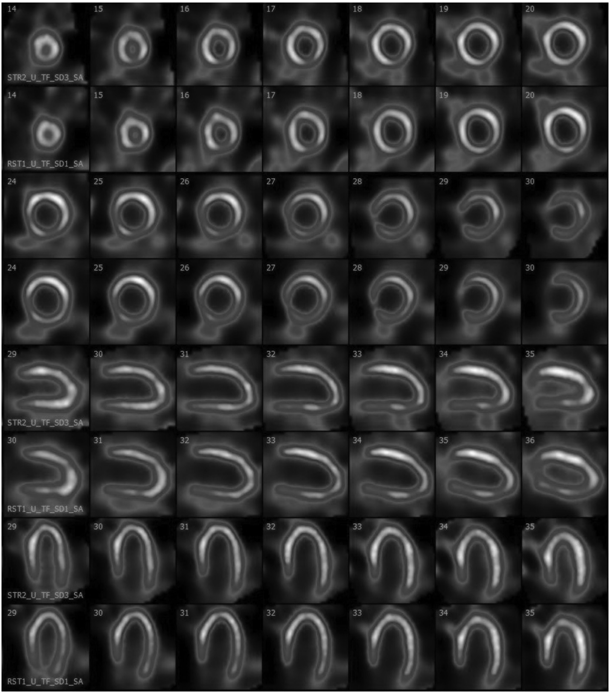
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Fig. 12.34 Normal myocardial perfusion scan using ^{99m}Tc-tetrofosmin. Stress images are positioned above the rest images. No perfusion mismatch is identified between stress and rest images. Top four rows represent the short-axis images. The next two rows represent the anterior, apical, and inferior walls. The final two rows represent the septum, and apical and lateral walls. (See also Colour plate.)

Image courtesy of Dr Nik Sabharwal.

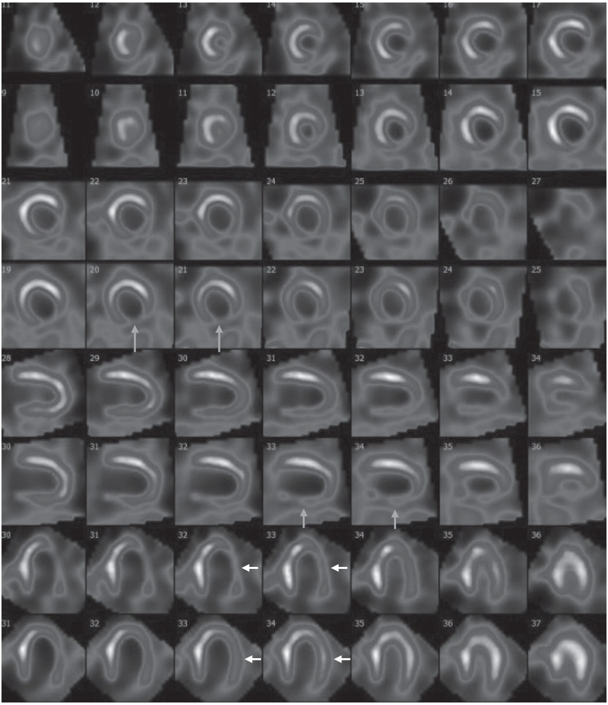

Fig. 12.35 Abnormal MPS scan (isotope: ^{99m}Tc-tetrosfosmin). Stress images above the resting images. Inferior hypoperfusion at rest confirming infarction (grey arrow). Lateral wall perfusion mismatch between rest and stress confirming a large volume of ischaemia (white arrow). RV prominence on stress scan is an adverse prognostic feature. (See also Colour plate.)

Image courtesy of Dr Nik Sabharwal.

Other nuclear cardiology investigations

Positron emission tomography

- In the past, PET was primarily considered a research technique, but its clinical use is growing.

Differences between SPECT and PET

Scanners

- Ring geometry of scanner and different detection methods.
- The ring scanner detects photons as coincidences.

Radioisotopes

- Short-lived radioisotopes (positron, rather than gamma, emitting), which have a half-life of minutes.
- The ring scanner can detect nano–picomolar concentrations of positron-emitting radiotracers.
- This ↓ the effective radiation dose.

Resolution

- The spatial and temporal resolutions are greater in PET than in other nuclear imaging techniques.
- PET scanners are more expensive, and PET tracers are less available.

Indications

Myocardial perfusion

- Offers higher resolution, lower radiation, and better diagnostic accuracy than SPECT MPS (90–93% specificity and 81–88% sensitivity).
- Can quantify myocardial blood flow and flow reserve by using products such as ^{15}O-water (diffuse into the myocardium proportionally to blood flow), ^{13}N-ammonia, and ^{82}Rb (actively extracted by myocytes).

Myocardial viability

- ^{18}F-deoxyglucose (FDG) utilization is reduced in areas of ischaemia. In hibernating myocardium, due to the lack of oxygen, fatty acid oxidation is reduced, and therefore, energy production is shifted to anaerobic glycolysis and preserved uptake of ^{18}FDG. There is therefore a mismatch between perfusion defects and ^{18}FDG uptake.

Myocardial inflammation/infection

- ^{18}FDG-PET can also be used to detect CV inflammation, as ^{18}FDG accumulates in highly metabolically active inflammatory cells.
- To suppress physiological uptake of ^{18}FDG, which may obscure the inflammatory signal from infection of structures near the myocardium, a high-fat, low-carbohydrate diet, fasting, or heparin load (to ↑ myocardial uptake of free fatty acid) is recommended.
- This technique can therefore help to detect conditions such as endocarditis, device infection, and sarcoidosis.
- In order to further differentiate between inflammation and infection, white blood cell (WBC) PET may be used. In this situation, there is uptake in leucocytes. Leucocytes are taken from blood, radiolabelled, and reinjected. Imaging is then performed at 4h and 24h. Accumulation of these leucocytes is highly specific for infection.
- In the future, there may also be a role for PET in identification of inflammation of plaques within the coronary arteries (see Figs. 12.36–12.39 and Colour plate).

Radionuclide ventriculography

- Equilibrium radionuclide ventriculography (ERNV) is used to assess LV function.
- The blood pool is labelled; a gated planar acquisition is obtained in an LAO projection to minimize overlap of the LV by other cardiac chambers. ROIs are drawn around the LV cavity in end-diastole and end-systole, together with an adjacent background ROI, allowing calculation of the EF.
- This provides an advantage over other techniques in that it is calculated by subtraction of end-systolic frames from end-diastolic frames, which do not assume that the LV is of a particular shape. This provides high reproducibility.
- The growth of echocardiography has led to a sharp decline in the number of ERNV studies performed. However, this technique may be useful where sequential measurements of the LV are required (e.g. post-chemotherapy).

^{99m}Tc-DPD scintigraphy

- ^{99m}Tc-labelled phosphate tracers, routinely used as bone scintigraphy agents, including 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), bind to amyloid protein and are taken up into the myocardium of individuals with cardiac amyloidosis.
- ^{99m}Tc-DPD is injected IV, and SPECT imaging performed at 3h to enable the tracer to reach the myocardium.
- Cardiac uptake is graded as: 0 = absent cardiac uptake, normal bone uptake; 1 = mild cardiac uptake, greater bone uptake; 2 = moderate cardiac uptake, similar to bone uptake; 3 = high cardiac uptake, minor/absent bone uptake (see Fig. 12.40).
- ^{99m}Tc-DPD scintigraphy is 100% sensitive and 86% specific for ATTR amyloid. Cardiac uptake is found in fewer than half of those with AL amyloid, making this an important tool to differentiate between the two.

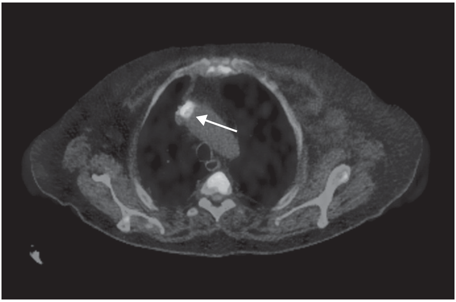

Fig. 12.36 Axial FDG-PET image. FDG avid uptake on the pacing lead in the superior vena cava at the level of the aortic arch. (See also Colour plate.)

Image courtesy of Dr Nik Sabharwal.

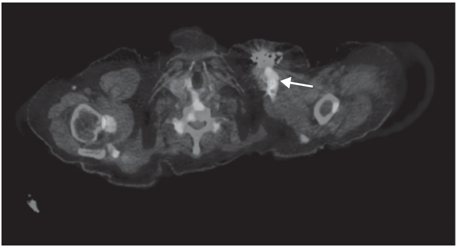

Fig. 12.37 Axial slice with FDG-avid area inferior to the implanted pacing device on the left. (See also Colour plate.)

Image courtesy of Dr Nik Sabharwal.

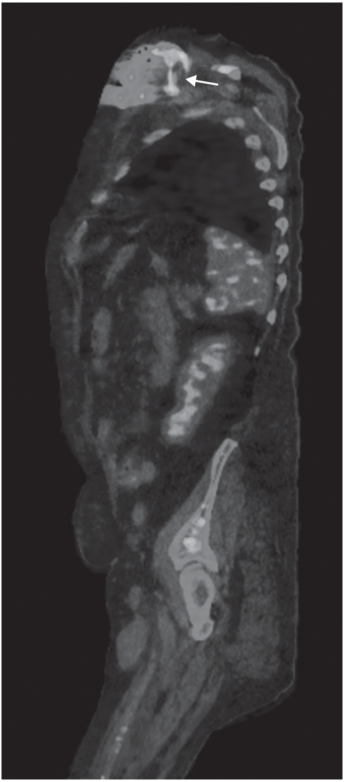

Fig. 12.38 Sagittal slice with FDG-avid area posterior to the implanted pacing device. (See also Colour plate.)

Image courtesy of Dr Nik Sabharwal.

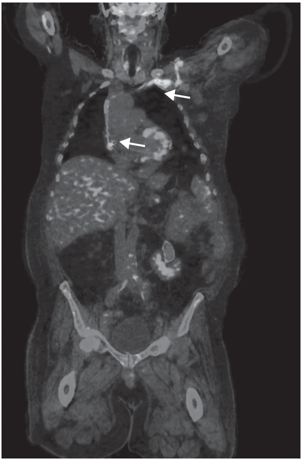

Fig. 12.39 Coronal slice with high FDG uptake over the pacing lead in the left subclavian area and tracking into the tissues towards the position of the pacing box (not seen). There is a further FDG-avid area overlying the lead in the right atrium near the tricuspid valve position. Non-specific cardiac uptake is identified. (See also Colour plate.)

Image courtesy of Dr Nik Sabharwal.

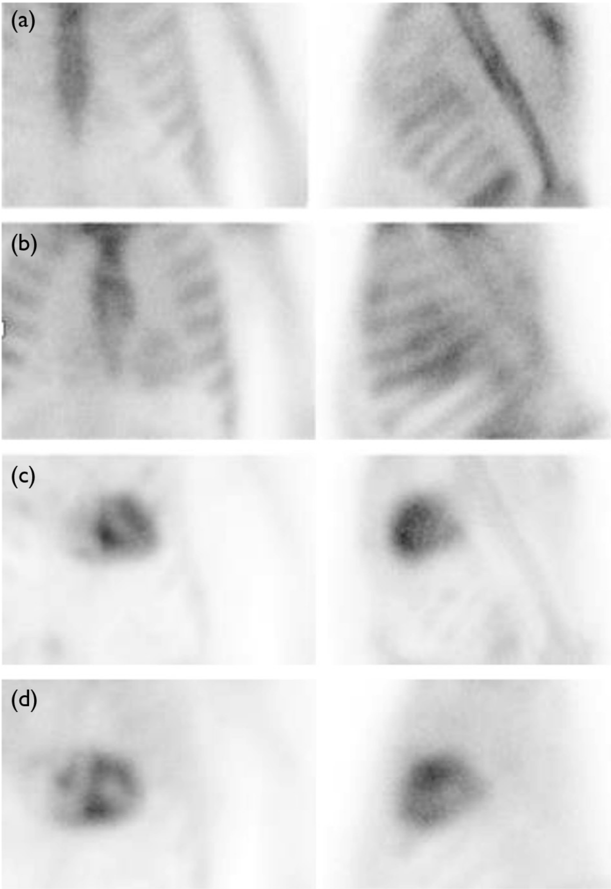

Fig. 12.40 Grades of uptake of ^{99m}Tc-DPD. (a) Grade 0: no cardiac uptake of the DPD tracer; normal bone tracer uptake in the sternum, ribs, and left arm on the coronal and lateral projections. Low likelihood of ATTR cardiac amyloidosis. (b) Grade 1: mild cardiac uptake of the DPD tracer; less obvious bone tracer uptake in the sternum, ribs, and left arm on the coronal and lateral projections. This does not exclude a diagnosis of cardiac amyloidosis. (c) Grade 2: cardiac uptake of the DPD tracer; suppressed bone tracer uptake in the sternum, ribs, and left arm on the coronal and lateral projections. High likelihood of ATTR cardiac amyloidosis. (d) Grade 3: significant cardiac uptake of the DPD tracer; almost non-detectable bone tracer uptake in the sternum, ribs, and left arm on the coronal and lateral projections; ↑ soft tissue uptake of the tracer. High likelihood of ATTR cardiac amyloidosis.

Image courtesy of Dr Nik Sabharwal.

Chapter 13

Coronary and structural interventions

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The cardiac catheterization laboratory

Effective team working is paramount in maintaining patient safety in the catheterization laboratory. Each member of the team must have a deep understanding of their role, be alert to any concerns or deterioration in the patient's status, and communicate these within the team effectively.

The team

- Interventional cardiologist.
- Scrub nurse/assistant nurse.
- Radiographer.
- Electrophysiology technician.
- Second or 'runner' nurse.

Catheterization laboratory layout

- The patient is placed in the centre of the room (see Fig. 13.1A).
- The interventionalist stands on the patient's right-hand side (see Fig. 13.1B).
- The c-arm generates and detects the X-rays (see Fig. 13.1C), and is above the patient at the start of the procedure, with a transparent radiation protector between the c-arm and the interventionalist (see Fig. 13.1D).
- The radiographer operates the c-arm and table position (see Fig. 13.1E).
- Data screens are visible in front of the interventionalist (see Fig. 13.1F).

Sterile procedures

- *Coronary intervention:* whilst coronary angiography/interventions are carried out with a sterile field close to the patient (i.e. sterile gloves and sterile gowns), the room itself is not necessarily considered to be a sterile environment, and therefore, hair protection and masks are not required.
- *Device implantation:* interventions where a device is implanted (structural/pacing procedures, but not stents) are carried out in sterile conditions. Masks and hair protection must be worn at all times by personnel in the catheterization laboratory during these procedures.

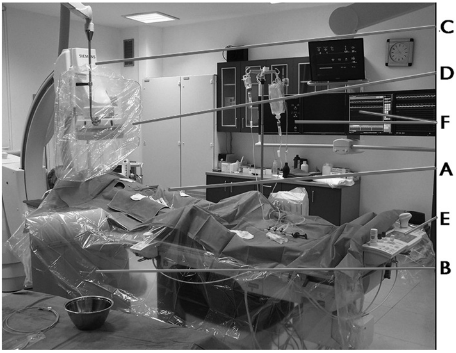

Fig. 13.1 Layout of a cardiac catheterization laboratory.

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Radiation protection

- All practitioners delivering ionizing radiation during medical procedures must attend the radiation protection course IR(ME)R (Ionizing Radiation Medical Exposure Regulations), 2017.
- Staff working in the catheterization laboratory should be issued with radiation-monitoring badges for the body and neck, which must always be worn whilst in the laboratory.
- These badges should be audited monthly to assess doses of radiation received by individual staff members.
- To protect individuals from unnecessary excess radiation, only essential staff should be in the catheterization lab during procedures.
- All staff should be as far from the radiation source as practical.

Minimizing patient dose

- Minimize screening and acquisition times.
- Keep the distance between the X-ray tube and the image intensifier to a minimum.
- Use collimation and cones to minimize the irradiated area.
- Use lower magnifications when possible.
- Use the lowest number of frames per second to allow adequate imaging.
- For prolonged procedures, the intensifier should be moved regularly, even by a few degrees, to try to minimize the possibility of skin burns.

Minimizing operator dose

- Lead aprons and lead collars should be worn.
- Additional screening should be used where available, such as a lead apron below the table, with a mobile lead screen to go between the operator and the source.
- Minimize X-ray exposure to the operator by reducing screening and acquisition time.
- Some projections (e.g. LAO) give much higher scatter of X-ray and operators should be aware of this.

The dose for an interventional cardiologist has been calculated as 60mSv (based upon 150 working days per year and four interventions per day). The calculated effective dose if the operator wears the correct lead apron and a thyroid collar is <5mSv per year. The maximum allowed dose is 20mSv per year.

Patient selection and prognostication

- In coronary disease, the decision between management with medical therapy, percutaneous revascularization, or surgery should be made on an individual basis.
- Such decisions should be made by using a multidisciplinary approach, with at least one member from the Heart Team having met the patient.
- Practitioners should carry out an objective prognostication risk assessment and have a discussion with the patient to ascertain which revascularization strategy is most appropriate.

Indications for coronary revascularization

- Elective coronary revascularization is indicated in symptomatic patients with significant CAD which has not responded adequately to medical therapy, and prognostically in the presence of significant coronary disease or ischaemia (see Box 13.1).
- Coronary revascularization should be guided by evidence of haemodynamically significant stenosis. The gold standard is either FFR or iFR, both of which are described in greater detail later in this chapter.
- Data from trials such as ISCHAEMIA and ORBITA suggest that contemporary medical therapy is effective at ↓ adverse events and may be comparable to revascularization in some instances.

Box 13.1 ESC recommendations for prognostic coronary revascularization

- >50% stenosis of left main coronary artery
- >50% stenosis of proximal left anterior descending artery
- >50% stenosis in 2/3 coronary arteries with left ventricular ejection fraction ≤35%
- Large area of ischaemia (>10% of myocardium)
- >50% stenosis in remaining patent coronary artery

Surgical risk assessment

- Surgical risk should be assessed at the earliest opportunity.
- Whilst Heart Team decisions should not be swayed solely on surgical risk scores, they are useful in assessing the appropriateness of percutaneous vs surgical approaches in challenging/complex cases.
- Widely used and established surgical risk score systems include: EuroSCORE II and the Society of Thoracic Surgeons (STS) Score. These tools estimate operative in-hospital or 30-day mortality.

SYNTAX score

- The SYNTAX score is a comprehensive method of objectifying complex coronary anatomy (see Box 13.2).

Box 13.2 SYNTAX score details

Lesions are graded on the presence of the following features:

- Dominance
- Number of lesions
- Segments involved by each lesion with lesion characteristics
- Number of occlusions
- Subtotal occlusions
- Character of collateralizations
- Bi-/trifurcation anatomy
- Aorto-ostial lesions
- Tortuosity
- Lesion length
- Calcification
- Presence of thrombus
- Whether diffuse disease is present

Situations where percutaneous coronary intervention may be preferable to coronary artery bypass graft

- Presence of comorbidity/frailty prohibiting recovery from surgery.
- Single or multivessel coronary disease with SYNTAX score ≤22.
- Chest deformity which may impact sternal wound healing.
- Previous chest radiotherapy which may ↑ surgical risk, impair internal mammary artery harvesting, and wound healing.
- Porcelain aorta.

Situations where coronary artery bypass graft may be preferable to percutaneous coronary intervention

- DM.
- Previous rapid or accelerated in-stent restenosis (ISR).
- Multivessel coronary disease with SYNTAX score ≥23.
- Poor peripheral arterial vascular access.
- Additional need for cardiothoracic surgery such as VHD.

Antiplatelet agents

The section below details commonly used antiplatelet agents, including some of the clinical evidence behind their use. For more details on these agents, see ➲ Antiplatelet agents: overview, p. 765.

Aspirin

- Aspirin inactivates cyclo-oxygenase 1 and COX-2.
- The beneficial effect of aspirin during PCI was shown in the Montreal Heart Study, in which treatment with aspirin and dipyridamole was superior to placebo in the prevention of peri-procedural MI.
- Low-dose aspirin (usually 75mg od), initiated at least 24h prior to the procedure, is recommended in patients undergoing PCI and continued lifelong in established CAD.

Thienopyridine P2Y$_{12}$ inhibitors

Ticlopidine

- Clopidogrel and ticlopidine are thienopyridine derivatives that inhibit platelet function independently of aspirin, by interfering with the platelet adenosine diphosphate (ADP) receptor.
- Early studies showed that DAPT with aspirin and ticlopidine was superior to aspirin alone.
- Use of ticlopidine was limited by potentially severe neutropenia.

Clopidogrel

- Clopidogrel has a safer side effect profile.
- The PCI-CURE (PCI—Clopidogrel in Unstable Angina to prevent Recurrent Events) study showed that pretreatment with clopidogrel (300mg loading dose, followed by 75mg daily), in addition to aspirin, for a median of 10 days before PCI, compared with aspirin alone, reduced the composite of CV death, MI, or urgent target vessel revascularization by 30% after 1 month.
- Most centres use high-loading dose clopidogrel (600mg) prior to elective PCI if the patient has not been preloaded.

Prasugrel

- Prasugrel is transformed into its active metabolite by hydrolysis and subsequent oxidation, and binds irreversibly with the P2Y$_{12}$ class of ADP receptors on platelets.
- Data from TRITON-TIMI-38 demonstrated that prasugrel therapy was associated with significantly ↓ ischaemic events, including stent thrombosis, but with an ↑ risk of major bleeding, including fatal bleeding in ACS patients treated with PCI. Overall mortality did not differ significantly between treatment groups.
- These data were supported by the ACCOAST trial, in which patients with NSTEMI were treated with prasugrel prior to PCI vs placebo, and subsequent post-PCI prasugrel if PCI was indicated. It was found that patients in the prasugrel pretreatment arm experienced significantly greater rates of TIMI (Thrombolysis in Myocardial Infarction) major bleeding.
- After a loading dose of 60mg, 10mg daily is continued for 1 year.
- Prasugrel should be used with caution in those at ↑ risk of bleeding.

Non-thienopyridine P2Y$_{12}$ inhibitors

Ticagrelor

- Ticagrelor is a reversible P2Y$_{12}$ receptor antagonist.
- Ticagrelor does not require conversion to a biologically active metabolite, unlike thienopyridines, and therefore reaches peak plasma concentration more rapidly than clopidogrel and prasugrel.
- The PLATO trial compared almost 19,000 patients with ACS treated with aspirin and either ticagrelor or clopidogrel. The study confirmed 1.1% absolute ↓ CV mortality and 1.4% ↓ all-cause mortality. There was a similar rate of fatal bleeding between the groups.
- Conventional treatment is 180mg loading dose, followed by 90mg bd thereafter.
- The development and introduction of ticagrelor have largely replaced the use of thienopyridines in pharmacological treatment of ACS.

Cangrelor

- Cangrelor is an IV non-thienopyridine inhibitor, which rapidly inhibits P2Y$_{12}$ receptors, with >95% inhibition of platelet aggregation at 15min.
- Cangrelor is unique in that it is the only IV preparation of a P2Y$_{12}$ inhibitor currently available, and it may have particular use in patients who are unable to orally consume tablets at the time of PCI.
- The phase II CHAMPION-PCI and CHAMPION-PLATFORM studies compared cangrelor with clopidogrel in the setting of ACS. Whilst the initial data suggested that cangrelor was not superior to clopidogrel in terms of hard CV outcomes, a post-hoc pooled analysis of the studies suggested that there is significant superiority with cangrelor in the composite of death, MI, and ischaemia-driven revascularization.
- CHAMPION-PHOENIX randomized patients with ACS and stable coronary disease to cangrelor or clopidogrel, and supported the post-hoc analysis of the two previous trials. It showed that cangrelor significant ↓ post-procedural stent thrombosis and peri-procedural MI.
- Cangrelor is given as a 30mcg/kg bolus injection, followed by a 4mcg/kg/min infusion for a maximum of 4h.

Adjunctive pharmacological therapies

Glycoprotein IIb/IIIa inhibitors

- The final common pathway for platelet aggregation is mediated by the platelet GPIIb/IIIa receptor.
- Antagonists of this pathway inhibit cross-linking of platelets, thereby ↓ platelet aggregation and inhibiting thrombus formation.
- Trials investigating PO preparations have not demonstrated meaningful benefits in CV outcomes.
- IV use is licensed in patients with ACS who are undergoing PCI. GPIIb/IIIa inhibitors should be considered as a bailout therapy if there are concerns over large thrombus burden or no reflow.

Abciximab

- Abciximab (e.g. ReoPro™) was the first GPIIb/IIIa inhibitor licensed.
- It is a Fab 7E3 monoclonal antibody, which binds to platelets.
- Clinical efficacy was tested in the EPIC trial, in which patients experienced a 35% ↓ in death, MI, or urgent/emergency revascularization; however, this was at the expense of significantly ↑ bleeding.
- Use of abciximab is not considered routine treatment in STEMI, as the BRAVE 3 trial showed no clear benefit in terms of infarct size or reinfarction at 30 days.
- A bolus dose of 0.25mg/kg is given by IV injection over 10min, followed by an infusion of 0.125mcg/kg/min for 12h.

Eptifibatide

- Eptifibatide (e.g. Integrilin™) is a cyclic heptapeptide, which is highly specific for GPIIb/IIIa.
- The ESPRIT trial compared eptifibatide to placebo, and the trial was terminated early owing to the superiority of the GPIIb/IIIa inhibitor; however, this was at the expense of ↑ bleeding.
- A 180mcg/kg bolus injection is given over 10min, followed by an infusion of 2mcg/kg/min for up to 96h.

Tirofiban

- Tirofiban (e.g. Aggrastat™) is a tyrosine-derived reversible antagonist of GPIIb/IIIa.
- A bolus 25mcg/kg injection is given over 3min, followed by a 150ng/kg/min infusion for up to 24h.

Direct thrombin inhibitors

Bivalirudin

- Bivalirudin (e.g. Angiomax™, Angiox™) is a direct thrombin inhibitor that exerts its activity by specifically and reversibly interacting with circulating (inactive) and clot-bound (active) thrombin.
- The HORIZONS-AMI and EUROMAX trials suggested bivalirudin was superior to GPIIb/IIIa inhibitors in STEMI, with ↓ bleeding complications.

- Clinical trials of bivalirudin in PCI have demonstrated similar benefits to the combination of abciximab and heparin, with ↓ clinically significant blood loss.
- However, contemporary data from the MATRIX and HEAT-PPCI trials suggested no superiority, when compared with UFH, and as a result, bivalirudin is now not routinely used in PCI.

Factor Xa inhibitors

Fondaparinux

- Fondaparinux is a pentasaccharide that binds to antithrombin and inhibits factor Xa, thereby reducing fibrin and thrombin generation.
- It is administered as a 2.5mg subcutaneous injection once daily.
- The OASIS-5 trial randomized NSTEMI patients to fondaparinux or enoxaparin, and demonstrated that patients treated with fondaparinux experienced more favourable CV outcomes, when compared with enoxaparin, with ↓ major bleeding. As a result, fondaparinux is widely used in the treatment of NSTEMI.

Unfractionated heparin

- Although there is general agreement that patients undergoing PCI should receive heparin before the intervention, there remains controversy regarding the issue of optimal dosage.
- An inverse relationship between the level of anticoagulation (measured by activated clotting time (ACT)) and the occurrence of acute ischaemic complications has been observed; however, >ACTs are associated with ↑ bleeding.
- A target ACT of >300s is often used in patients undergoing PCI.
- LMWH (enoxaparin) has been shown to be effective in PCI; however, it has not replaced UFH in routine use.

Radial vascular access

- A radial approach is the preferred access route for coronary angiography.
- There are several advantages, including ↓ vascular complications, the ability to mobilize patients immediately following their procedure, and discharge earlier than after femoral access procedures.
- Patient selection for radial access should include palpation of the radial artery to confirm vessel patency.

The procedure for obtaining radial access is outlined in Box 13.3.

Box 13.3 Procedure for the radial artery approach

- Consent the patient.
- Remove all jewellery from the arm; shave the area and disinfect.
- For local anesthesia, use 2–5mL of 2% lidocaine via a 25-gauge needle (enough to anaesthetize, but not to distort the anatomy).
- The artery should be palpated with the index and middle fingers, with the index finger lifted and the artery punctured at 45°.
- The artery should be punctured as proximally as possible, and care should be taken to avoid the flexor retinaculum (the anatomy is summarized in Fig. 13.2).
- Once pulsatile flow is obtained, a guidewire can be advanced through the needle and into the vessel lumen.
- Make a small incision in the skin to allow passage of an arterial sheath. Care should be taken not to damage the radial artery while making this incision.
- Use the blade to incise in the longitudinal plane, rather than transversely, to ↓ the risk of completely transecting the artery.
- A variety of long and short sheaths are available. The advantage of long sheaths is that they minimize trauma to the radial artery.

Complications

Radial artery spasm is the commonest complication of radial artery puncture and sheath introduction. There are various techniques to try and prevent radial artery spasm from occurring; these include:

- Careful patient selection, avoiding small arteries
- Adequate patient sedation if required—pain provokes spasm
- The use of a ‘cocktail’ of drugs introduced directly into the radial artery. Many different regimens have been described (e.g. 1mg isosorbide dinitrate, 2.5mg verapamil, and 2500U heparin made up to 10mL with 0.9% saline). There is limited evidence of an effect of these regimens in ↓ spasm, and their use is operator-dependent.
- Repeated doses of nitrates or verapamil (up to 5mg) given directly into the sheath may be required
- Shorter sheaths may be better tolerated
- Some sheaths have a hydrophilic coating to try to reduce spasm and induce ↓ discomfort on removal.
- Always use a guidewire to straighten catheters prior to removal from the aortic arch through the radial sheath.

Common radial pitfalls and solutions

Radial loop

- 360° loop in the radial artery.
- This may be negotiated with a hydrophilic guidewire or an angioplasty wire before straightening with a catheter.
- Alternatively, a change of access point to the left radial artery or femoral artery may be required.

Tortuosity in proximal vessels

- This also may be negotiated as above.
- Manoeuvres such as breath-holds and gentle ipsilateral arm traction may help.

Recurrent radial artery

- An anatomical variant arising from the radial artery below the elbow, which may be blind-ending.
- Contrast injection may provide a useful roadmap.

Difficulty accessing the ascending aorta

- Breath-holding may help to straighten the access route.

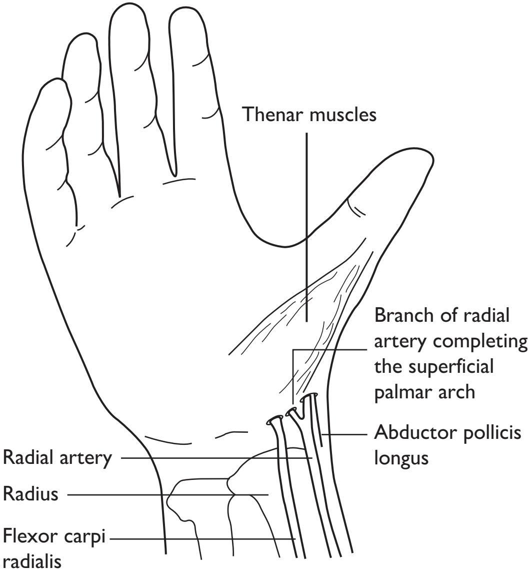
Thenar muscles
Branch of radial artery completing the superficial palmar arch
Abductor pollicis longus
Radial artery
Radius
Flexor carpi radialis

Fig. 13.2 Radial artery anatomy.

Femoral vascular access

- Seldom used in coronary angiography unless there are difficulties with accessing the radial artery; used in some CABG cases (see Box 13.4).
- The femoral artery is the preferred access for structural interventions (others include the apical approach, subclavian, and carotid TAVI).
- Femoral artery access is associated with ↑ bleeding complications.

Box 13.4 Procedure for femoral artery access

- The artery is located by palpating below the inguinal ligament, the ideal position for puncture being within 3cm below the inguinal ligament and slightly lateral to the position of the vessel (anatomy summarized in Fig. 13.3).
- Vascular US recommended to ↓ complications.
- Puncture into the artery should be made above the bifurcation with the profunda femoral and superficial bifurcation.
- Anaesthetize the area with local anaesthetic (10mL of 2% lidocaine).
- Warn the patient that 'pins and needles' or transient numbness may occur in the leg. This is caused by the effects of lidocaine directly on the femoral nerve.
- A small incision (3–5mm) is made in the skin. The tissue incision may then be dilated by using curved 'mosquito' forceps.
- Puncture the artery by using the Seldinger technique. A hollow needle is introduced slowly. It is often possible to feel the pulsations of the artery via the needle before the vessel is punctured.
- When the needle is introduced into the vessel, pulsatile flow confirms its position in the arterial lumen.
- A 0.035" wire is advanced into the vessel through the needle.
- Withdraw the needle whilst leaving the wire in, and introduce a haemostatic sheath (usually 5–8Fr diameter) over the wire.
- Withdraw the wire once the sheath is in place.

Sheath removal

- Can be performed immediately after the procedure or delayed if high doses of heparin are administered such as in complex/multivessel PCI.
- Haemostasis can be achieved by manual compression or by using a compression device (e.g. Femstop™).
- Closure devices (e.g. Angioseal™ or Perclose™) allow early mobilization following procedure and may ↓ bleeding complications.

Femoral artery dissection

- Often caused by wire advancement into the femoral artery wall.
- This can be avoided through gentle advancement of the wire down the bore of the femoral artery needle and stopping if any resistance is felt.
- If there is difficulty advancing catheters or sheaths, use hydrophilic wires to negotiate difficult anatomy.
- Dissections are diagnosed prior to closure with fluoroscopy.
- Treatment is often conservative. If there are concerns over compromise to the leg, an urgent vascular surgical opinion should be sought.

Femoral artery pseudoaneurysm

- Caused by incomplete haemostasis after the procedure.
- Review the access site after closure—expanding masses may represent haematoma; if bleeding persists, a pseudoaneurysm can result.
- US is used to diagnose and may require thrombin injections.

Distal embolization

- Due to plaque disturbance, air injection, or thrombus embolization.
- It is imperative to minimize plaque disturbance by advancing catheters and sheaths over wires; withdraw all air from equipment, and use heparinized saline throughout the procedure.
- Can be diagnosed clinically as an acute stroke or as pale, pulseless, and painful arms/legs.
- Requires stroke team intervention or vascular surgical input.

Retroperitoneal haemorrhage

- Rare and potentially devastating complication, which occurs with high punctures of the femoral artery (above the inguinal ligament).
- Can also occur with transection of the femoral artery at the time of puncture whereby bleeding enters the retroperitoneal space.
- If significant blood loss occurs, the patient could experience circulatory collapse and require large-volume blood transfusion.
- Diagnosis is often by CT.
- Conservative treatment (blood products, volume expanders) is normally sufficient. Surgical repair of the vessel is sometimes required.

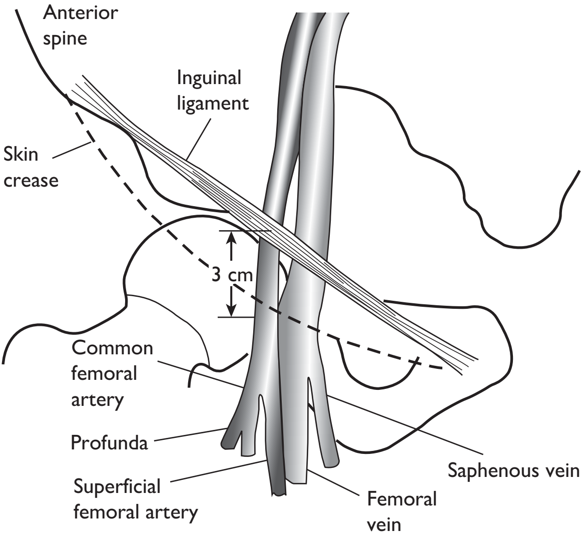

Fig. 13.3 Anatomy of the inguinal canal. The femoral vein lies medial to the femoral artery. The puncture should be made 3cm below the inguinal ligament.

Vascular closure devices

Radial haemostasis

- Radial sheaths are removed immediately as the position of the artery renders compression simpler.
- Compression bands (RadiStop®, Radi Medical Systems USA; TR-Band™, Terumo) are generally used (see Fig. 13.4).

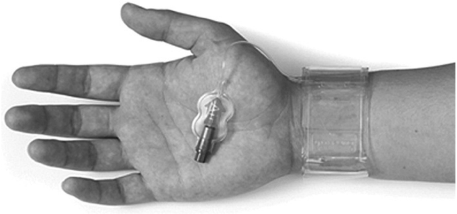

Fig. 13.4 TR-Band™. Radial access closure device.

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How to place a TR-Band™

- Position the spot on the TR-Band™ over the radial puncture site, with the sheath *in situ*.
- An assistant should inflate the syringe with the minimal amount of air (usually 12–15mL) needed to achieve haemostasis, while ensuring the radial artery remains palpable.
- The operator withdraws the sheath from the radial artery.
- Add/remove additional air if needed.
- Perform regular neurovascular hand observations.
- Deflate the TR-Band™ over a few hours until bleeding has stopped.

Femoral haemostasis

- Sheaths should only be removed by trained members of staff.
- After coronary angiography, when no or little heparin is given, the sheath may be removed immediately, provided a closure device is used.
- Direct pressure should be applied just proximal to the site of the skin puncture for 5–10min.
- After angioplasty, an ACT of <150s suggests that the effect of systemic heparinization is wearing off and it is acceptable for the sheath to be removed.
- Femoral clamps (FemoStop®, Radi Medical Systems) can be used to ↓ bleeding in patients.

Vascular closure devices

- Historically, mechanical compression was the only method for controlling bleeding from vascular access sites in the groin.

- Increasingly complex procedures have necessitated the need for larger sheaths, which has ↑ the risk of bleeding and made achieving haemostasis more challenging.
- Various closure devices have been introduced—the aim of these is to ↑ patient comfort and ↓ complications.

Suture-based closure devices

- Perclose® (Abbot Vascular, USA): this delivers a suture to the arterial puncture site.
- The device is sheath-like; needles are positioned above the sheath in the handle and are deployed by a plunger. A 'clincher' that performs a knot-tying function completes a sliding knot.
- StarClose® features a Nitinol® clip that is designed to promote the primary healing process to achieve secure closure of the femoral artery access site following vascular procedures.
- This provides 360° tissue apposition for rapid healing/haemostasis.

Collagen-based closure devices

- These devices use a bioresorbable collagen plug deposited at the arteriotomy site via a sheath.
- These include Angio-Seal® (St Jude Medical, USA; see Fig. 13.5) and VasoSeal® (Datascope Corp, USA).

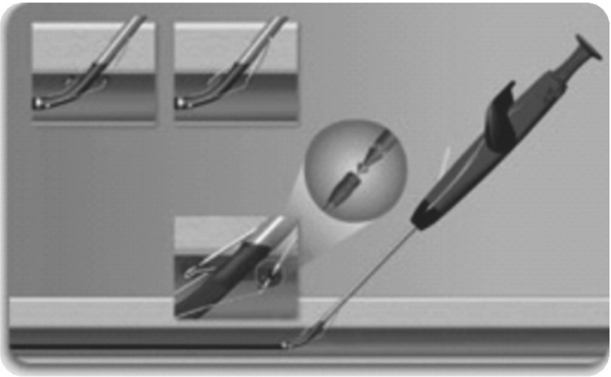


Fig. 13.5 Angio-seal® vascular closure device.

Drug-based closure devices

- Clo-Sur® PAD (Medtronic, USA): this device contains a naturally occurring biopolymer polyprolate acetate. This polymer has a coagulant property when brought into contact with heparinized blood.
- The device is placed on the puncture, and the haemostatic sheath removed. Direct pressure is applied until haemostasis is achieved.

Coronary angiography

Pre-shaped coronary angiographic catheters

- Catheters used in diagnostic coronary angiography come in a variety of preformed shapes (see Fig. 6.7).
- In the UK, the most commonly used pre-shaped catheters are the Judkins Left (JL) 3.5 ('3.5' is the distance in centimetres between the primary and secondary catheter curves) and the Judkins Right (JR) 4. These are used to image the LCA and RCA, respectively.
- Pigtail catheters, used for left ventriculography, are also used.
- The diameter of catheters are measured in French gauge (Fr); catheters between 4Fr (0.053") and 8Fr (0.105") are commonly used.

Catheter advancement and manifold usage

- A 'J'-tipped 0.035" guidewire is placed within the flushed catheter.
- The catheter is then passed into the haemostatic sheath.
- The guidewire is advanced ahead of the catheter under fluoroscopic guidance until it reaches the aortic root, just above the aortic valve.
- The catheter is advanced to this position.
- The guidewire is removed.
- To ensure that no air or clot is within the catheter, a small volume of blood is aspirated from the catheter into a syringe and discarded.
- The catheter is carefully connected to a 2-way manifold to allow pressure monitoring, saline flushing, and contrast injection through a closed system.

Contrast injection

- Great care must be taken at all times to ensure that air is not injected into the coronary arteries.
- The injection syringe should be filled with contrast from the reservoir, and then the syringe held with the plunger elevated such that any air bubbles rise to the top of the syringe.
- Contrast should then be injected at a continuous rate, aiming to fully opacify the coronary artery.
- The pressure trace must be normal prior to injection.
- Pressure damping suggests an ostial stenosis, excessively deep intubation, or selective intubation of a branch.

Contrast must not be injected if there is evidence of pressure damping.

Coronary angiography/left ventriculography

Left coronary artery

- The 50° left anterior oblique (LAO 50) is the preferred projection for cannulation of both the left and right coronary ostia.
- In reality, however, the left coronary ostium is often cannulated in the anteroposterior (AP) position.
- The JL3.5 catheter will almost invariably cannulate the left coronary ostium with minimal manipulation.
- If the catheter is delivered to the non-coronary or right coronary sinus, to engage the left main coronary artery in a co-axial orientation, the catheter should be pulled back to the level of the left main coronary artery (which lies slightly higher than the RCA ostium) and rotated clockwise.
- In patients with large aortic roots (large, hypertensive patients), a JL4 or JL5 (with a larger curve) may be needed.

Right coronary artery

- The LAO 50 projection is preferred for cannulation of the right coronary ostium.
- The JR4 catheter is introduced to the aortic root until it lies 1–2cm above the aortic valve.
- The catheter is then rotated ('torqued') in a clockwise direction, such that the catheter tip rotates towards the right coronary ostium.
- It may be necessary to reduce the torque to prevent the catheter from overshooting.
- There is often lateral movement as the catheter enters the artery.
- Before contrast is injected, it must be ensured that the pressure tracing transduced from the tip of the catheter is not damped.
- Damping can suggest that the catheter has selectively intubated the conus branch of the right coronary artery, and injection of contrast into this vessel can induce ventricular arrhythmias.

Left ventriculography

- Position a pigtail catheter a few centimetres above the aortic valve.
- Pull the wire back 5–10cm to make the catheter tip soft, and push gently (the catheter may cross at this point).
- If the catheter does not cross, apply torque and pull the catheter back and the tip should cross the valve.
- If this is not successful, use a straight, soft-tipped guidewire and catheters that allow that guidewire to be 'pointed' at the valve (AL1 or JR4).
- Once the catheter is in a stable (free of ectopy) position in the mid-left ventricular cavity, connect to the manifold and measure the pressure.
- Disconnect the manifold catheter connected to the power injector, and expel all air.
- Set the injection rate—typically 25–30mL of contrast at 10mL/s.
- Warn the patient about hot flush and the feeling of extra beats.
- When the left ventriculography has been performed, the catheter is reconnected to the manifold to allow pressure recording as the catheter is withdrawn across the aortic valve (the pullback pressure).

Coronary catheters

Fig. 13.6 shows common cardiac catheter shapes and their names.

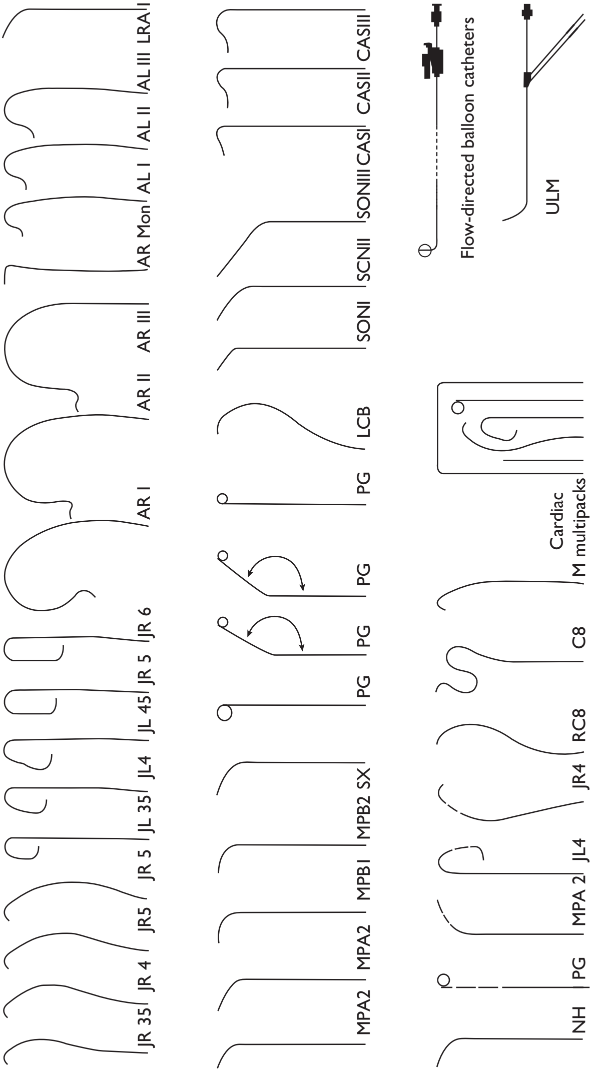
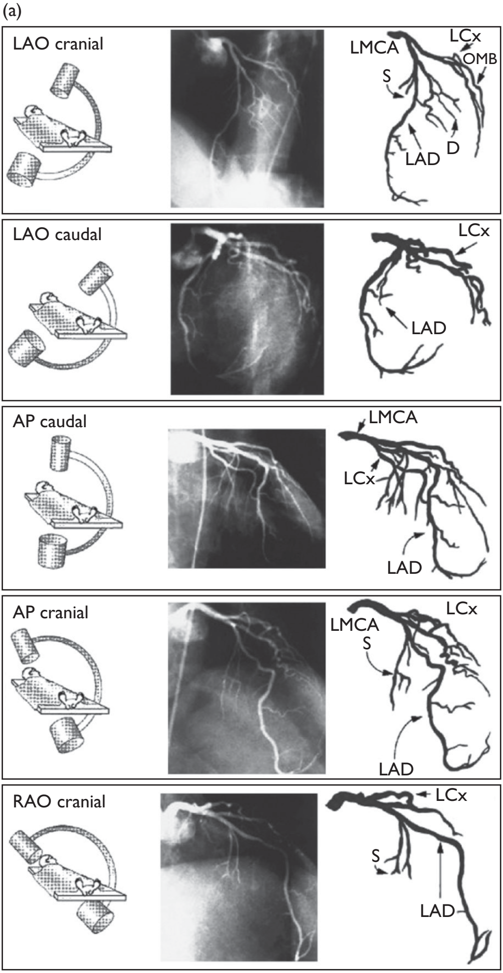

JR 35
JR 4
JR5
JR 5
JL 35
JL4
JL 45
JR 5
JR 6
AR I
AR II
AR III
AR Mon
AL I
AL II
AL III
LRA I
MPA2
MPA2
MPB1
MPB2 SX
PG
PG
PG
PG
LCB
SONI
SCNII
SONIII
CASI
CASII
CASIII
NH
PG
MPA 2
JL4
JR4
RC8
C8
M multipacks
Cardiac
Flow-directed balloon catheters
ULM

Fig. 13.6 Common cardiac catheter shapes and their names.

Interpretation of the coronary angiogram

Standard image intensifier positions and their resulting angiographic views for visualization of the coronary arteries are outlined in Fig. 13.7.


(a)
LAO cranial
LMCA
LCx
OMB
S
D
LAD
LAO caudal
LCx
LAD
AP caudal
LMCA
LCx
LAD
AP cranial
LCx
LMCA
S
LAD
RAO cranial
LCx
S
LAD

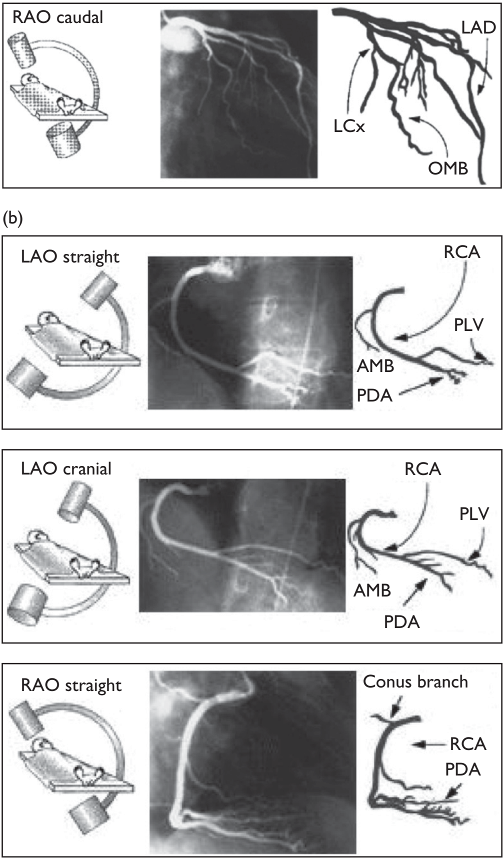

RAO caudal
LAD
LCx
OMB
(b)
LAO straight
RCA
PLV
AMB
PDA
LAO cranial
RCA
PLV
AMB
PDA
RAO straight
Conus branch
RCA
PDA

Fig. 13.7 (a) Left coronary artery and (b) right coronary artery angiographic views.
Braunwald E (ed) (2001). *Heart Disease: a textbook of cardiovascular medicine*. 5th ed. Philadelphia: WB Saunders.

Angiographic study of coronary artery bypass grafts

- It is important to study the surgical record/operation note to ascertain how many grafts were placed at the time of the operation.
- Sometimes useful information (often from a surgeon's operation note) can be obtained as to the position in the ascending aorta from which the grafts arise.
- Leftward-facing grafts are best cannulated from the right anterior oblique (RAO) 50 projection.
- Rightward-pointing grafts are best cannulated in the LAO 50 projection.
- It may be necessary to perform aortography to visualize the position of the grafts.
- Specialist catheters (such as the left coronary bypass (LCB) catheter) have been designed to aid in cannulation of grafts and there is usually a predictable anatomy (see Box 13.5).

Box 13.5 Coronary artery bypass graft anatomy

- Posterior descending artery grafts originate from the right anterior aspect of the aorta and run vertically to the inferior surface of the heart.
- Obtuse marginal grafts originate from the left anterior aspect of the aorta and arc towards the posterolateral surface of the heart.
- Left anterior descending and diagonal grafts originate from an intermediate position and run laterally towards the anterior interventricular groove.

Left internal mammary artery grafts

- Arterial grafts improve patency rates in CABG and are preferred in contemporary surgery.
- Left internal mammary artery (LIMA) grafts are usually accessed via the femoral route but may also be accessed via the left radial approach.
- Right internal mammary artery (RIMA) grafts are less often used and can be approached via either the femoral or right radial route.
- The left subclavian artery is accessed by using a standard JR or multipurpose catheter. Care must be taken when advancing catheters up the subclavian artery.
- A JR catheter may engage the LIMA directly or may need to be exchanged over a long wire for an internal mammary artery catheter.
- Small contrast injections may be used to identify the LIMA ostium.
- Coronary injections should be acquired in different orthogonal planes to adequately visualize the LIMA and its subtended territory, particularly at the point of insertion.
- The patient should be warned that they may feel a warm flushing feeling in their arm and neck.
- The catheter should be disengaged under fluoroscopic screening and carefully removed over a wire.

Common aortic positions for placement of saphenous vein graft

The common graft positions are outlined in Fig. 13.8.

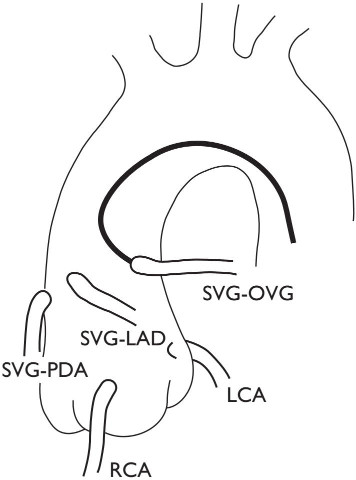


Fig. 13.8 Common aortic positions for placement of saphenous vein graft. OVG, omniflow vascular graft.

Reproduced with permission from Braunwald E (ed) (2001). *Heart Disease: a textbook of cardiovascular medicine*. 5th ed. Philadelphia: WB Saunders.

Intravascular ultrasound

- IVUS is a technology that allows direct visualization of atherosclerotic plaque and vessel lumen, which can assist in clinical decision-making.
- IVUS images can give insights into the underlying plaque histology.
- The full endovascular circumference of the vessel wall is seen, not a two-dimensional surface as in angiography, and is thus the method of choice to determine the vessel luminal area (see Fig. 13.9 and Colour plate).
- Useful in imaging ambiguous lesions such as intermediate lesions of unknown severity, ostial stenosis, LMS disease, and disease at bifurcation sites (see Box 13.6).
- Images the plaque, not just the lumen.
- Allows optimal results during angioplasty and stenting.

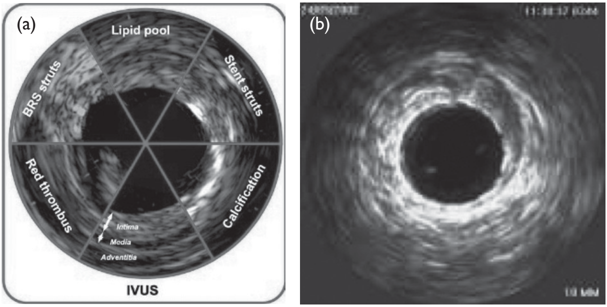


Fig. 13.9 (a) Example of image obtained by intravenous ultrasound (IVUS). (b) IVUS image of a coronary stent. (See also Colour plate.)

(a) Reproduced from Ono M *et al*. *Front Cardiovasc Med*. 2020; 7: 119 under Creative Commons CC BY 4.0 ☞ https://creativecommons.org/licenses/by/4.0/. Copyright © 2020.

Intravascular ultrasound technology

- US images are produced by passing an electrical current through a piezoelectric crystal that expands and contracts to produce sound waves.
- Sound waves are reflected from tissues and return to the transducer, where they are detected and converted to an electrical impulse that can be presented graphically.
- A phase array of crystals is used, and these are sequentially activated to produce circumferential imaging.
- The equipment required to perform an IVUS examination involves a miniaturized US transducer mounted on a catheter (2.6–3.5Fr) and a computer interface that carries out image reconstruction.

Box 13.6 Intravenous ultrasound technique

- Intracoronary isosorbide dinitrate and IV heparin are administered.
- The IVUS catheter should be carefully advanced distal to the area of interest.
- A motorized pullback device is then used to draw the IVUS catheter proximally at a fixed speed.
- Landmarks such as side branches can be useful.
- Positions may also be recorded angiographically.

Clinical data

- IVUS has been subject to several large-scale randomized clinical trials in patients with single-vessel, complex multivessel, bifurcation, and LMS disease.
- The consensus from ADAPT-DES, AVIO, CORBIS, IRIS-DES, MAIN-COMPARE, MATRIX, and RESET is that US-assisted PCI is associated with more favourable CV outcomes, including ↓ reinfarction, stent thrombosis, and death.

Intravascular ultrasound and vulnerable plaques

- It has become apparent from IVUS studies that non-obstructive and haemodynamically insignificant atherosclerotic plaques can be responsible for sudden death due to MI.
- These high-risk or vulnerable plaques cannot be differentiated by angiography alone and can consequently be left untreated.
- IVUS can assist in identification of these high-risk plaques, ensuring they are treated correctly.

Histopathological features of vulnerable plaque

- Lipid-rich core.
- Thin, fibrous cap.
- Necrotic core.
- High degree of macrophage infiltration.

Advantages with intravascular ultrasound

- Able to discriminate ↓ (lipid) and ↑ (fibrous) echodensity plaques.
- Able to identify the capsule.
- Able to identify areas of rupture within the plaque.
- In combination with image analysis, information regarding the tissue types imaged can be derived, to provide a plaque histology map.
- Able to assess stent apposition and furthermore assess whether a stent has been adequately deployed at the time of PCI.

Optical coherence tomography

- Uses near-infrared light and fibreoptic technology to acquire high-resolution images of the internal structure of coronary arteries during coronary angiography and PCI.
- Light is emitted from the catheter and reflected off the internal structures of the artery.
- The reflected light is then collected back through a transparent sheath near the tip of the catheter, inside which lies a rapidly rotating optical fibre.
- The light is converted into electrical signals, which are interpreted by computer software, and a reconstructed image is created in real time (see Fig. 13.10 and Colour plate).

Principal uses of optical coherence tomography

- High axial resolution means that optical coherence tomography (OCT) is ideal for high-resolution imaging of microstructures not visible by IVUS such as identification of plaque rupture, cap erosion, and thrombus.
- High-risk plaque characterization, including cap thickness estimation, plaque eccentricity, lipid pool analysis, necrotic core estimation, and plaque inflammation (macrophage accumulation).
- Real-time quantification of minimal luminal area for stent insertion.
- Interrogation of apposition post-stent insertion and assessment following stent failure.

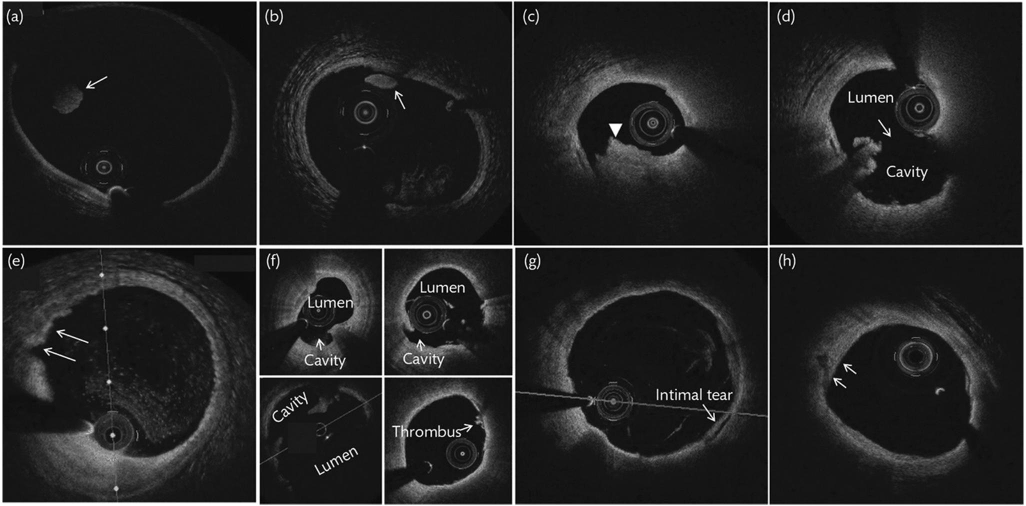

(a)
(b)
(c)
(d)
Lumen
Cavity
(e)
(f)
Lumen
Cavity
Lumen
Cavity
Cavity
Lumen
Thrombus
(g)
Intimal tear
(h)

Fig. 13.10 Optical coherence tomography images. (a) Red thrombus; (b) white thrombus; (c, d) plaque rupture; (e) plaque erosion; (f, g) ruptured caps, cavity, thrombus, and intimal tear; (h) friable tissue in the saphenous vein graft. (See also Colour Plate.)

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Physiological assessment of coronary flow

- Angiography alone provides a two-dimensional image of the artery lumen.
- Even if two orthogonal views are used, they are limited in their ability to confirm if a lesion is culpable for downstream myocardial ischaemia.
- As an epicardial artery becomes more stenotic, both coronary blood flow and flow reserve (ratio of maximum to basal flow) ↓.

Fractional flow reserve

- FFR is the ratio of maximum blood flow in the presence of a stenosis, compared with flow in the absence of stenosis.
- In epicardial CAD, coronary flow correlates with pressure, hence the term 'pressure wire assessment'.
- A specially designed wire with a pressure probe is placed before and after the lesion to assess pressure (and derived flow).
- FFR must be measured in maximum hyperaemia to simulate maximum blood flow; this is achieved by administering adenosine.
- During the infusion, pressure is measured distally (P_d, distal pressure) and proximally (P_a, proximal pressure), and the ratio is expressed as the FFR (see Fig. 13.11a, in unobstructed artery; see Fig. 13.11b in diseased artery).
- FFR allows an on-the-spot diagnosis as to what extent a given stenosis contributes to myocardial ischaemia and can guide decisions regarding revascularization.
- At present, the best-established indication for coronary FFR estimation is as a diagnostic tool to assess severe coronary narrowing, and for this, it is sensitive when used with a cut-off point of $\leq$0.80 (an example of user interface shown in Fig. 13.12 and Colour plate).
- FFR has also been used to optimize the results of stent implantation.

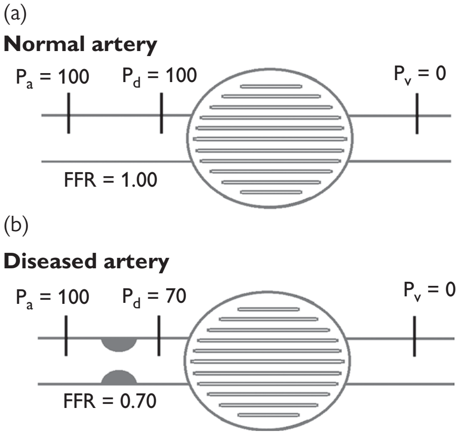

Fig. 13.11 FFR measurement in normal (a) and diseased (b) arteries.

The FAME study

- This randomized, prospective, multicentre trial (FFR vs Angiography for Multivessel Evaluation) investigated 1005 patients with multivessel CAD 12 months after receiving a stent, and compared outcomes where treatment was guided by FFR with where treatment was guided only by angiography.
- Results demonstrated a statistically significant 30% ↓ in major adverse cardiac events (MACE) in the FFR arm and was cost-effective with ↓ repeat procedures.

Instantaneous wave-free pressure ratio

- FFR requires the use of adenosine to induce a state of fixed hyperaemia. Adenosine is not required with iFR, as a period of diastole is used where the aortic and distal microcirculatory pressures equilibrate (hence the name wave-free) to measure the pressure ratio of the stenotic lesion.

The DEFINE-FLAIR and iFR SWEDEHEART trials demonstrated that iFR-guided revascularization was non-inferior to FFR with a cut-off of <0.89.

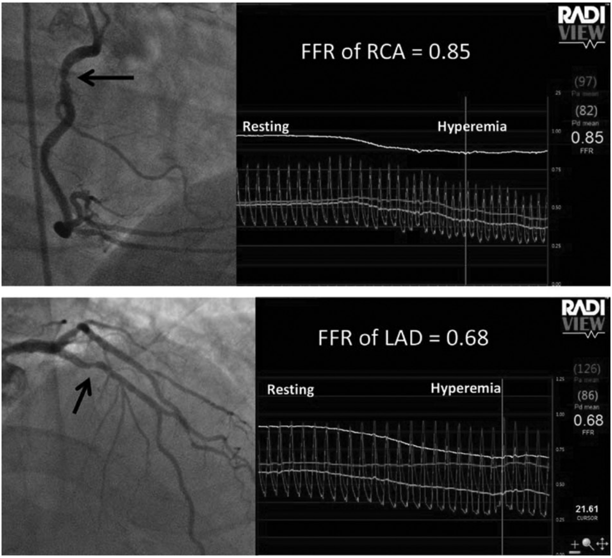
RADI VIEW
FFR of RCA = 0.85
(97)
Pa mean
Resting
Hyperemia
(82)
Pd mean
0.85
FFR
RADI VIEW
FFR of LAD = 0.68
(126)
Pa mean
Resting
Hyperemia
(86)
Pd mean
0.68
FFR
21.61
CURSOR

Fig. 13.12 Examples of coronary angiograms, with associated intracoronary flow assessments by FFR. (See also Colour plate.)

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Balloon angioplasty and coronary artery stenting

Balloon angioplasty

- Before stents became widely used in the 1990s, balloon angioplasty was the commonest percutaneous treatment for coronary artery narrowing.
- Vessel dissection and thrombosis/restenosis were common after balloon angioplasty. As a result, plain old balloon angioplasty (POBA) has been superseded by coronary stent implantation.
- Balloon angioplasty is rarely used in select patients in whom delivery of a stent is not possible from an anatomical perspective, or if there are concerns over prolonged antiplatelet therapy (see Box 13.7).

Box 13.7 Balloon angioplasty procedure

- Consent the patient.
- Cannulate the artery with the chosen guiding catheter. Ideally, the guiding catheter should be coaxial with the coronary ostium (thus allowing maximum support and minimizing trauma to the vessel).
- A steerable 0.014" guidewire is introduced to the catheter via the haemostatic valve. The tip of the guidewire may be pre-shaped; however, many operators prefer to take a straight guidewire and shape the tip by hand.
- Using fluoroscopy and contrast to delineate the coronary anatomy, the guidewire is advanced along the vessel beyond the narrowing and placed as distally as possible in the vessel.
- An appropriately sized balloon is then selected, based on lesion size. The balloon selected should be longer than the lesion.
- The guiding catheter can be used as a reference when sizing the vessel. For calcific lesions and ISR, shorter balloons with more highly rated burst pressure may be better.
- The balloon is advanced along the guidewire to the correct position.
- In some situations, it may prove difficult to pass the balloon to the desired position, and deeper insertion of the guide catheter or a more supportive guide catheter may be needed.
- Radio-opaque markers are used to position the balloon accurately. Inflation should be undertaken with fluoroscopic screening to ensure that the balloon does not move.

Implantation of coronary stents

- The primary function of a stent is to act as a scaffold to maintain vessel patency; implantation is often carried out after balloon angioplasty of a vessel.
- It is preferable to implant coronary stents after balloon angioplasty, as this reduces the risk of acute vessel closure and restenosis (see Box 13.8).
- Much of the success of stents is primarily due to their mechanical ability to produce large gains in lumen dimensions.

Box 13.8 Stent delivery procedure

- Consent should be gained before the procedure.
- The vessel is normally prepared by pre-dilating the lesion with balloon angioplasty (see Box 6.7).
- A stent, which is preloaded on a deflated balloon, is then passed over the coronary wire.
- The stent size is determined by the lesion length and is generally longer than the pre-dilation balloon.
- The stent is advanced to the desired lesion with fluoroscopy and inflated to deploy.
- The balloon is deflated and removed from the vessel (see Fig. 13.13).
- Fluoroscopy is used to assess the result.
- The stent is often further dilated with a non-compliant balloon taken to high pressure to ensure the stent is well apposed to the vessel wall.

- Stents can be made of stainless steel, cobalt-based alloy, tantalum, nitinol, or polymer; however, the majority of stents used today are made of stainless steel and balloon-mounted.
- Common drug coatings on DES include sirolimus, paclitaxel, and everolimus.

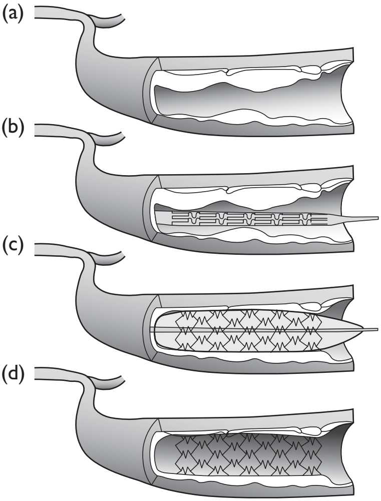

Fig. 13.13 Coronary stenting. Wire introduced across the lesion (a); stent positioned (b); stent deployment (c); balloon removed (d).

Angioplasty in multivessel coronary artery disease

- Multivessel coronary artery disease (MVD) is a term used to describe significant atherosclerosis in two or more coronary arteries.
- Clinical trials had demonstrated that PCI with balloon angioplasty and bare metal stents (BMS) was inferior to CABG for MVD in terms of relieving angina and freedom from repeat procedures.
- Contemporary trials show that PCI with DES can be an appropriate alternative, even with MVD in some patients.

SYNTAX

- SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Coronary Surgery) was a prospective, randomized, multicentre trial including 'all-comers', as well as those with complex LMS and complex three-vessel disease.
- A total of 1800 patients from Europe and the USA were randomized to multivessel PCI with TAXUS™ DES or CABG, based on the revascularization strategy decision of a Heart Team, including an interventional cardiologist and surgeon.
- The only exclusion criteria were prior revascularization, acute MI, or the need for concomitant cardiac surgery.
- The SYNTAX scoring system should be used to risk-stratify patients and help with decision-making for complex revascularization cases.
- The study showed that at 1 year, there was ↑ repeat revascularizations in the PCI group (13.5% vs 5.9%); however, rates of clinically significant graft or stent closure were remarkably similar.
- There was a statistically significant excess of strokes in the CABG group (2.2% vs 0.6%).
- In less complex anatomy, PCI is favourable (score ≤ 22).
- In more complex anatomy, CABG is favourable (score ≥ 23).

Procedural considerations in multivessel percutaneous coronary intervention

- The decision to proceed should be made by the Heart Team.
- Revascularizing multivessel coronary artery disease requires pre-procedural planning.
- SYNTAX score and EuroSCORE should be carried out to assist with clinical decision-making; however, surgical risk assessment should not be used as the sole decision-making tool.
- Consider the patient's comorbidity and anaesthetic risk.
- Consider vascular access routes and whether percutaneous coronary interventionis feasible.
- Coronary artery bypass grafting is preferred in diabetic patients.
- Are there reasonable targets for placement of grafts?
- Does the patient require concomitant cardiac or thoracic surgery?
- Is the patient likely to recover from sternotomy and be compliant with physical therapy or dual antiplatelet therapy after percutaneous coronary intervention?

Left main stem intervention

- Management of LMS CAD has been subject to extensive debate.
- Traditionally, CABG has been preferred in all patients.
- The NOBLE and EXCEL trials have supported the notion that PCI may be a reasonable alternative in some patient groups.
- The advent of DES and lower rates of ISR, compared with PCI with BMS, has further changed the approach towards PCI and away from CABG.

SYNTAX left main stem subgroup analysis

- There was no difference in all-cause deaths between PCI and CABG groups (4.2% vs 4.4%) and MI (4.3% vs 4.1%).
- There was an excess of strokes in the CABG group and a reduction in repeat procedures.
- The 2-year MACE rates remained significantly higher for PCI than for CABG, mainly driven by higher repeat revascularization in the PCI arm.
- MACE rates at 2 years were not significantly different for patients with a low (0–22) or intermediate (23–32) baseline SYNTAX score treated with either PCI or CABG.
- For patients with high SYNTAX scores (≥33), MACE rates continued to be ↑ at 2 years in patients treated with PCI, compared with CABG.
- In the LMS group, safety outcomes and MACE rates were similar for PCI and CABG, but the 2-year revascularization and MACE rates favoured CABG.

NOBLE and EXCEL

- These two contemporary non-inferiority studies were a head-to-head comparison of the latest-generation stents vs coronary artery bypass surgery.
- Whilst the data generated from these trials suggest that LMS PCI may be a suitable alternative in some patients, as demonstrated by the non-inferiority of PCI vs CABG, there were significant questions posed about particular aspects of the studies designs and also the noted ↑ MACE with PCI.
- It should be noted therefore that whilst CABG remains the gold standard for LMS disease, with/without the addition of MVD, PCI can be a reasonable alternative in some patients after careful consideration by the Heart Team.

Procedural considerations

- Nothing less than an excellent angiographic result is acceptable.
- IVUS may be utilized pre-procedure to ascertain the true vessel diameter, and post-procedure to ensure that stents have been adequately deployed.
- LMS bifurcations may be approached by using conventional bifurcation techniques.

Chronic total occlusions

- A chronic total occlusion (CTO) is defined as a coronary occlusion known to be >3 months old.
- Only about 10% of PCIs are performed for CTO, with the majority of patients being referred for CABG, which remains the 'gold standard' for CTO revascularization.
- The main reason that CTO PCI fails is high procedural complexity, with failure of wire passage through the point of occlusion being the commonest reason.
- CTO PCI carries an ↑ risk of complication owing to ↑ procedure length, often comorbid patients, and the presence of dense calcification which can make wire and catheter behaviour unpredictable.
- Nearly half of patients with significant CAD on coronary angiography have at least one CTO.
- CTO training has become an additional training barrier for interventional cardiology registrars, and this ought to be undertaken in a high-volume centre to gain the necessary skills.
- Procedural success improves with operator experience; ↓ volume centres may wish to perform the procedures either on site, with more experienced CTO operators present, or transfer care of the patient to a high-volume centre.
- Comorbid patients and the presence of dense vascular calcification can sometimes make wire and catheter behaviour unpredictable.

Factors that improve procedural success

- Experienced operator(s).
- Use of specialist equipment such as dedicated CTO wires and microcatheters.
- Procedural planning with cardiac CT.

Predictors of procedural failure

- Longer length of occlusion.
- Longer duration of occlusion.
- Presence of calcification.
- Presence of bridging collaterals.
- Blunt (as opposed to tapered) stump at the point of occlusion.
- Presence of a side branch at the point of occlusion.
- Vessel tortuosity.

Use of stents in chronic total occlusion

- Stent implantation improves CTO intervention outcomes, compared with balloon angioplasty alone.
- Recanalized CTO vessels still have a relatively ↑ rate of restenosis.

This has been ↓ by the use of DES, with improved efficacy of DES demonstrated in several randomized controlled trials.

Procedural considerations in percutaneous coronary intervention for chronic total occlusion

- A normal approach to CTO PCI involves a planned, progressive escalation in the equipment chosen to tackle the occlusion.
- A femoral approach using 8Fr guiding catheters is often chosen, such that guide catheter support can be optimized.
- Begin with softer wires such that the occlusion may be probed, before moving on to stiff wires that may allow the cap of the occlusion to be penetrated.
- Over-the-wire balloons and microcatheters may ↑ the chances of successful wire penetration. If the occlusion is crossed, the occlusion can be dilated and treated with stent implantation in a conventional manner.
- Stent implantation with DES improves CTO intervention outcomes, compared with balloon angioplasty alone.

Wiring techniques in percutaneous coronary intervention for chronic total occlusion

- Antegrade dissection re-entry technique (see Fig. 13.14).
- Side-branch technique.
- Parallel wire technique.
- Subintimal re-entry technique.
- IVUS-guided recanalization technique.
- Retrograde approach (see Fig. 13.14).

Complications associated with chronic total occlusions

These procedures are often lengthy and involve significant radiation and contrast exposure. Thus, complications are not infrequent and this must be considered when gaining consent. Complications may include:

- Impairment of collateral flow
- Retrograde dissection
- Perforation
- Guidewire entrapment
- Subacute vessel re-occlusion
- Extensive contrast use, resulting in contrast-induced nephropathy.
- ↑ radiation exposure.

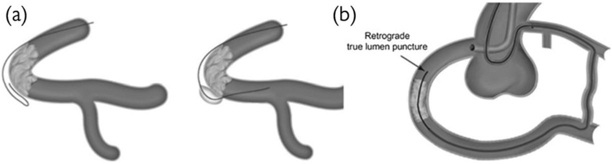

Fig. 13.14 Antegrade dissection and re-entry technique (a), and retrograde collateral technique (b).

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Bifurcation lesions

- Bifurcation lesions are associated with ↑ rates of restenosis when compared with conventional lesions.
- A bifurcation lesion involves a side branch with a reference diameter of ≥2mm.
- IVUS studies show that plaque in the main vessel almost invariably extends some distance into side branches.
- Angioplasty will often cause plaque shift into the side branch.

Procedural considerations in bifurcation percutaneous coronary intervention

- The majority of operators adopt a ‘simple’ provisional strategy in which the main branch stent is implanted and the side branch only treated in the event of its occlusion or dissection.
- Two-stent techniques, such as ‘T’ stent, ‘culotte’, ‘crush’, ‘mini-crush’, and ‘shotgun’, are shown in Fig. 13.15.
- Unless flow in the side branch is severely impaired or the ostium is severely narrowed during treatment of the main vessel, a single-stent technique is preferable to use of two stents.
- Dilating with a balloon through the struts of a stent carries the risk of deforming the distal stent and failure of adequate apposition of the stent to the vessel wall.
- Poor stent apposition ↑ the risk of thrombosis and restenosis, and thus a final ‘kissing’ balloon should be used.
- Dedicated bifurcation stents exist; however, the complexity of delivery has resulted in the rare use of these specialist stents.

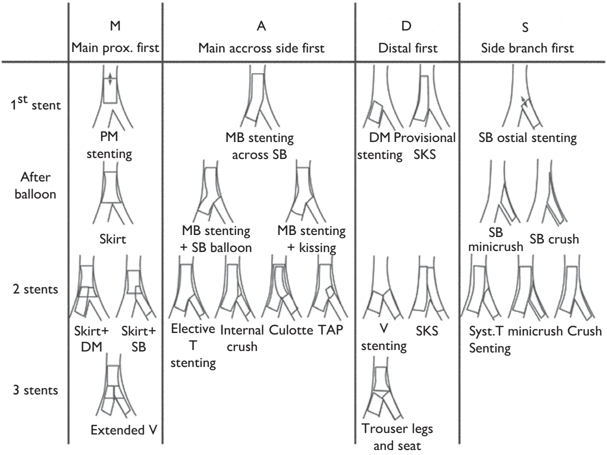
M
Main prox. first
A
Main accross side first
D
Distal first
S
Side branch first
1st stent
After balloon
2 stents
3 stents
PM stenting
Skirt
Skirt+ DM
Skirt+ SB
Extended V
MB stenting across SB
MB stenting + SB balloon
MB stenting + kissing
Elective T stenting
Internal crush
Culotte
TAP
DM stenting
Provisional SKS
V stenting
SKS
Trouser legs and seat
SB ostial stenting
SB minicrush
SB crush
Syst.T Senting
minicrush
Crush

Fig. 13.15 Common bifurcation stenting strategies.

The Medina classification

- The Medina classification is the convention by which bifurcation lesions are described.
- This is based on the presence of atheroma in the proximal main branch, distal main branch, and side branch (see Fig. 13.16).

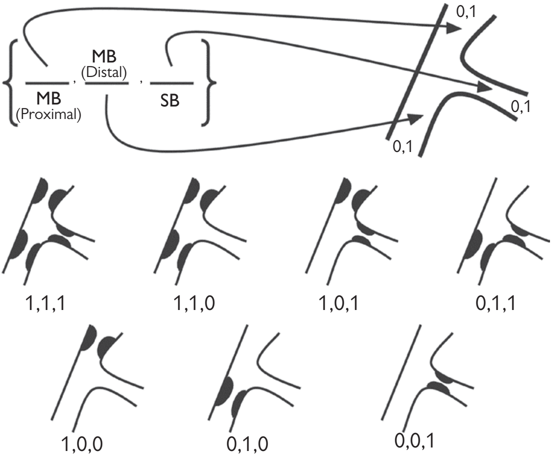
MB
(Proximal)
MB
(Distal)
SB
0,1
0,1
0,1
1,1,1
1,1,0
1,0,1
0,1,1
1,0,0
0,1,0
0,0,1

Fig. 13.16 The Medina classification.

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Primary angioplasty in ST-segment elevation myocardial infarction

- Chest pain and ST-segment elevation on a 12-lead ECG signify complete proximal epicardial coronary artery occlusion and STEMI.
- Occur as a result of rupture or erosion of a vulnerable atheromatous plaque, leading to platelet activation and adhesion, formation of platelet-rich thrombus, fibrin deposition, and red cell entrapment.
- If untreated, myocardial necrosis commences ≤30min, affecting full myocardial thickness ≤6h.

Treatment of STEMI

- PPCI is the preferred reperfusion strategy where angiography can be performed within 90min of presentation (see Box 13.9).
- Urgent restoration of coronary blood flow (reperfusion) prevents further myocardial necrosis and improves prognosis.
- Whilst not all hospitals have a 24h PCI facility, patients can be transferred to PPCI centres (example of PPCI shown in Fig. 13.17).

Box 13.9 Treatment options for STEMI

Primary percutaneous coronary intervention

- PPCI to culprit vessel angioplasty and stent implantation achieves full arterial patency (Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow) in 90–95%.
- Treats the occlusive thrombus and culprit plaque.

Thrombolysis

- Administration of a fibrinolytic agent (thrombolysis)
- Achieves full arterial patency (TIMI grade 3 flow) in 50–60%
- Contraindicated in up to 30% of patients
- Does not treat plaque rupture

Rescue PPCI

- Urgent culprit vessel PCI performed when fibrinolysis has failed to achieve reperfusion
- Often requires patient transfer to regional PPCI centre if persistent ST-segment elevation and pain

Indications for emergency reperfusion in STEMI

- ST-segment elevation in two consecutive chest leads (see Box 13.10).
- LBBB and 'true posterior' MI are not clear PPCI indications; however, some centres do include these.
- Chest pain onset ≤12h.

Pre-procedure checklist

- Verbal consent is sufficient.
- Analgesia and antiemetic (e.g. morphine 5–10mg, metoclopramide 10mg).
- Oxygen if saturations <94%.
- Aspirin 300mg PO (loading dose).
- Ticagrelor 180mg PO (loading dose).

Box 13.10 ECG findings in STEMI

New ST-segment elevation at J-point in two contiguous leads is significant if:

- ≥1mm in leads other than leads V2/V3
- In leads V2/V3:
  - Women ≥1.5mm
  - Men <40 years, ≥2.5mm
  - Men ≥40 years, ≥2.0mm

Procedural considerations in PPCI

- Radial access is associated with lower bleeding complications.
- The leg can be prepared in cases of profound haemodynamic instability or arrhythmia where an intra-aortic balloon pump or a temporary pacing wire may be required.
- Culprit vessel percutaneous coronary intervention is prognostic.
- Other vessels may be treated to provide complete revascularization; however, data are conflicting on whether this provides prognostic benefit.

TIMI grade flow

The TIMI grades coronary flow as follows:

- TIMI 0—occlusion of culprit artery, with no distal vessel flow.
- TIMI 1—some proximal contrast flow, but no distal vessel filling.
- TIMI 2—perfusion of entire artery, but sluggish flow.
- TIMI 3—perfusion of entire artery, with normal flow.

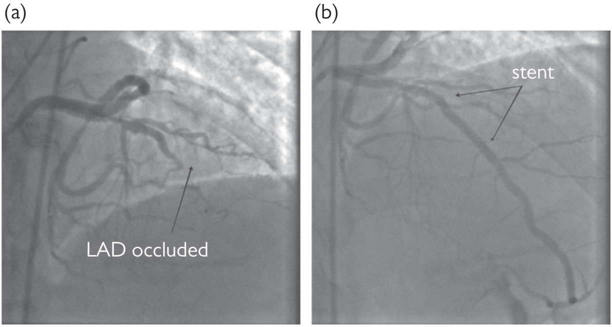

Fig. 13.17 Angiographic images from a patient with ST-segment elevation myocardial infarction. Left anterior descending (LAD) artery is occluded mid vessel (a). The same artery is now widely patent following primary percutaneous coronary intervention (b).

Bare metal stents, drug-eluting stents, bioresorbable vascular scaffolds, and drug-coated balloons

- Balloon angioplasty originated from Switzerland in 1977 by Dr Andreas Grüntzig.
- The major drawbacks of POBA include acute vessel closure, dissection, and ↑ restenosis.
- POBA was superseded by BMS in 1986.
- BMS are associated with ↑ ISR.
- DES have become widely used in conjunction with DAPT (see Fig. 13.18).

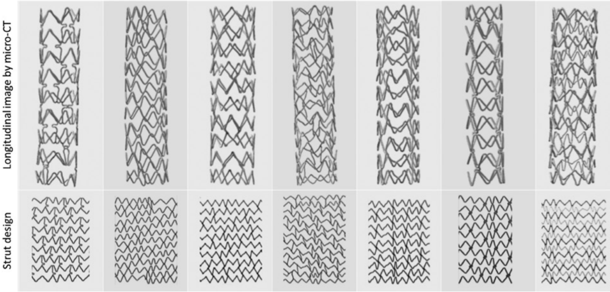

Fig. 13.18 Stent structure (applicable to BMS and DES).

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Bare metal stents

- First-generation metallic stents were made with 316L stainless steel.
- Contemporary stents are based on cobalt–chromium and platinum–chromium alloys, which have facilitated the development of struts of <100 microns, with no significant loss in tensile strength.
- Metallic stents can also have various coatings, which have useful clinical indications such as a PTFE membrane (covered stents) for coronary artery perforation.
- BMS are very rarely used in contemporary practice, owing to the development of DES.
- Conventional practice had been to use BMS in instances where there may be concerns over prolonged DAPT. However, even in these cases, DES are non-inferior to BMS.

Drug-eluting stents

- DES are coated with anti-proliferative agents, which reduce the rates of ISR.
- Similarities between tumour growth and benign neointimal proliferation introduced the concept that immunosuppressive and cytotoxic agents might be beneficial in preventing ISR.
- Incorporating these agents into stent coatings has enabled delivery of the active agent directly to its site of action, which limits systemic side effects.
- ↑ numbers of patients who would have otherwise only been suitable for CABG have successfully undergone multivessel PCI with DES.
- DES has facilitated PCI in complex LMS and bifurcation cases that would have otherwise been inappropriate with POBA or BMS.
- Randomized controlled trial evidence shows rates of target lesion revascularization (TLR) at 1 year for procedures carried out with DES to be <5%, compared with 10–25% for procedures that used a BMS.
- Commonly used contemporary agents are zotarolimus and everolimus.

Bioresorbable vascular scaffold

- Bioresorbable vascular scaffolds (BVS) were developed as a successor to DES.
- In theory, BVS have been designed to dissolve after drug delivery and restore vessel pulsatility that would otherwise have remained absent if BMS/DES were used.
- It could also allow further PCI/surgical revascularization without concerns over layering of stent struts or targets for CABG.
- Several iterations of the device have been developed, and while short-term data suggested promising results, medium- and long-term follow-up data from the ABSORB trials suggest ↑ rate of late thrombosis compared with contemporary DES.
- Currently, BVS are not routinely implanted as a result of these data.

Drug-coated balloons

- Drug-coated balloons, or drug-eluting balloons (DEBs), are not currently widely used in *de novo* CAD but are used in ISR or stent malapposition.
- In theory, use of DEBs will provide an additional layer of anti-restenotic drug, most commonly paclitaxel or sirolimus; however, large-scale randomized clinical trials comparing them with stents are still awaited and their use is limited to select cases.

Cutting balloons, rotational atherectomy, lithotripsy, and laser devices

- A number of alternative devices have been developed to assist with complex calcific lesions.
- Laser, rotational, and directional atherectomy catheters and cutting balloons make up some of the devices which can be used in particularly heavily calcified lesions, ISR, and ostial lesions.

Cutting balloon

- Cutting balloons are similar to conventional angioplasty balloons, with the addition of three (2.0mm and 2.5mm balloon) or four (≥3.0mm balloon) microtome surgical blades.
- The balloon is folded to shield the blades and protect the vessel wall as the catheter is passed to and from the lesion.
- As the cutting balloon is inflated, the microtomes expand radially and incise the plaque, facilitating maximum dilatation of the target lesion with the least amount of force, resulting in controlled injury, in contrast to irregular and unpredictable intimal injury associated with regular balloon angioplasty.
- Additional care must be taken to avoid dissection and vessel occlusion. Fig. 13.19 shows a cutting balloon.

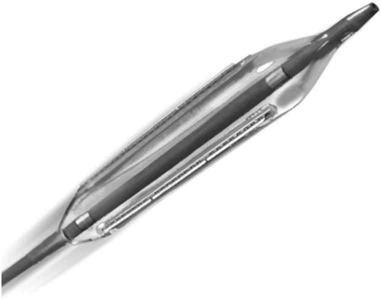

Fig. 13.19 An inflated cutting balloon on a coronary wire. The microtome surgical blades lie on the surface of the balloon, and upon inflation, the blades excise plaque.

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Rotational atherectomy

- Rotational atherectomy (also known as rotablation atherectomy, after the Rotablator™ system, SciMed/Boston Scientific) catheters have irrigated diamond-tipped burrs.
- Burrs rotate at up to 200,000rpm and preferentially remove hard tissue, thus preparing a lesion for subsequent stenting.
- Useful in the liberation of severe calcific stenosis in particularly calcified disease.

- Ideal for when failed attempts have been made at preparing the vessel with conventional balloons.
- A dedicated rota-wire is passed down the vessel, onto which the radio-opaque atherectomy device is advanced.
- Use of this device is widespread and can be used in a variety of presentations such as bifurcation and LMS calcification. Fig. 13.20 shows an atherectomy burr.

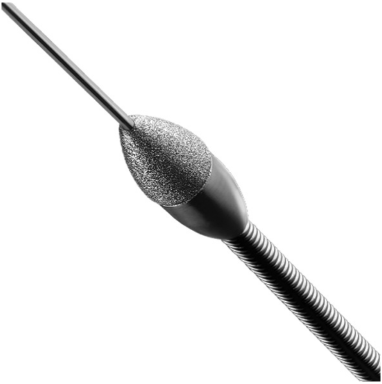

Fig. 13.20 An atherectomy burr loaded onto a rota guidewire. The burr can be sized, depending on the vessel lumen, and ranges from 1.25mm to 2.5mm. The burr is made up of a driveshaft (lower part of the image) and the diamond-tipped burr (distal hemisphere of the device).

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Lithotripsy

- Lithotripsy can be useful in extensive calcific coronary disease.
- Conceptually, the method by which this works is similar to that in renal and ureteric stones.
- The Intravascular Lithotripsy (IVL) ™ system (Shockwave Medical) relies on sonic energy waves, transmitted through a balloon, which locally fractures calcific disease, thereby preparing the vessel for stenting.

Laser

- Laser technology is used in complex CAD.
- Laser is not used directly on the endothelial surface; rather it is used to generate bubbles from superheated water, which generates intense localized heat to lyse calcific disease and prepares the vessel for stenting.
- Whilst no clinical trial has yet demonstrated a clear benefit with laser over conventional PCI, it can be used in some long calcific non-dilatable lesions where other conventional measures to prepare the artery have failed.

Embolic protection devices

- Distal embolization of plaque debris, thrombus, and fibrin during balloon inflation and stent deployment is recognized as a cause of suboptimal results after PCI.
- Vein grafts and thrombotic lesions are now recognized as being particularly prone to complications arising from distal embolization, such as the 'no-reflow' phenomenon which is seen in up to 30% of vein grafts that contain thrombus at the time of PCI.
- Whilst not routinely used, these distal protection devices can be considered in select cases.
- Devices can be broadly split into those that occlude the conduit distally and then allow aspiration of debris, or distal filters that capture debris downstream. However, there are limitations to these techniques (see Box 13.11).

Box 13.11 Limitations of distal protection devices

- Lack of randomized controlled trial demonstrating clear benefit
- Incomplete filter apposition or incomplete conduit occlusion
- Lack of protection of side branches
- Distal ischaemia with balloon occlusion devices

Balloon occlusion devices

- Balloon occlusion devices provide a physical barrier to debris and thrombus embolization. The PercuSurge Guardwire™ is one of the most commonly used and is made of three parts.
  - The Guardwire™ temporary occlusion catheter, which is placed distally in the vessel to allow occlusion
  - The microseal adapter that allows control over inflation and deflation of the balloon
  - The export aspiration catheter, which allows collected debris to be aspirated into a 20mL syringe (see Fig. 13.21).
- One of the main disadvantages of this system is that the target vessel is temporarily occluded, and thus the distal myocardium may be rendered ischaemic.

Filter devices

- The Angioguard™ device consists of an angioplasty guidewire, with an expandable filter at the distal tip. The filter can be expanded once the target lesion has been crossed.
- Antegrade flow in the vessel is maintained, and displaced debris should theoretically be collected in the filter. The filter is then collapsed and withdrawn into the retrieving catheter.
- The FilterWire™ device consists of a fish-mouth opening distal filter, mounted on an angioplasty guidewire. The mouth of the filter, in theory, expands to fill the entire lumen of the vessel. The filter is deployed by withdrawing a delivery sheath and collected into a retrieval sheath, as shown in Fig. 13.22.

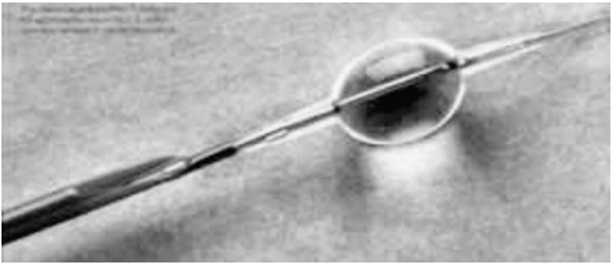

Fig. 13.21 Balloon occlusion device for distal protection. Much like an angioplasty balloon, inflation of this device occludes the vessel and limits blood flow and debris embolization. However, the surface is designed such that little vessel wall plaque is disturbed during inflation.

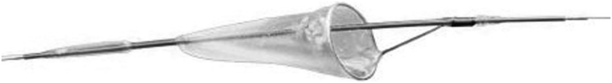

Fig. 13.22 FilterWire™. The distal wire can be seen at the top of the image, with the filter opening and the proximal portion of the device at the bottom. Blood flows through the filter, and debris are collected in the net prior to withdrawal.

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Haemodynamic support devices

Intra-aortic balloon pump

- First used clinically in the late 1960s, IABPs were the first developed support device to be used in patients with myocardial ischaemia.
- The device is a long balloon on a guidewire, which is fed, by the femoral artery, into the aorta.
- The balloon inflates in diastole and ↑ coronary perfusion. This can ↑ myocardial contractility in ischaemia, and by extension ↑ CO.
- *Indications:* whilst there are no clear indications for use (as demonstrated by the lack of randomized controlled data positively correlating their use with improved survival), they can be inserted at the discretion of the interventionalist.
- *Contraindications:* significant AR as ↑ diastolic filling can cause circulatory collapse.
- *Limitations:* reliant on a stable intrinsic heart rhythm; will not assist patients with persistent unstable arrhythmias.

Extracorporeal membrane oxygenation

- Occasionally used as a temporary bailout for cardiopulmonary collapse and as a bridge to emergency CABG or heart/lung transplant.
- ECMO unloads the RV, and then after removal of carbon dioxide and red cell oxygenation, blood is either reinserted to the arterial (VA-ECMO) or venous system (VV-ECMO), as shown in Fig. 13.23.
- The device requires femoral arterial and venous access. The patient is anticoagulated and is therefore at risk of major bleeding.
- ECMO is often inserted in specialist centres and performed by perfusion interventionalists and trained support nurses.
- *Indications:* unable to wean off cardiopulmonary bypass, graft rejection/graft failure in heart transplant, and severe cardiogenic shock.

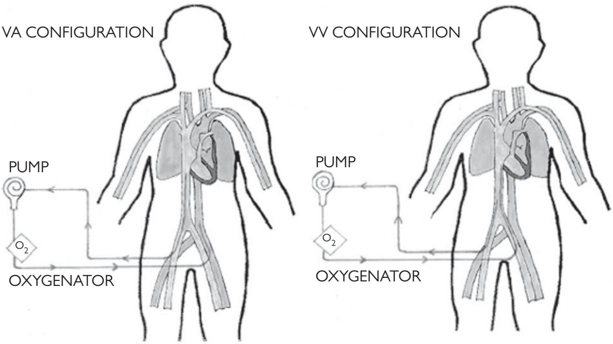

Fig. 13.23 Venoarterial (VA) and venovenous (VV) extracorporeal membrane oxygenation configurations.

Reproduced from Shekar K *et al*. *Journal of Critical Care* 2012; **27**(6):741.e9–741.e18 with permission from Elsevier.

- *Contraindications:* irreversible cardiac disease (or no available/appropriate destination therapy), malignancy, brain injury/death, trauma.
- *Limitations:* limited site training and availability; high risks of thrombosis, bleeding, and limb ischaemia.

Percutaneous left ventricular assist devices

- LVADs can be inserted as a bridge to transplant/destination therapy.
- The patient must be anticoagulated to ↓ the risk of thromboembolism.
- Large-bore arterial and venous catheters are inserted, often via a femoral approach, and fed into a primed external centrifugal pump, which has the capacity to deliver ≥4L/min blood flow.
- Newer LVAD systems can be placed directly in the thoracic cavity.
- Blood is not filtered or oxygenated, and with modern insertion techniques, patients can be mobile after insertion.
- The device can also be inserted into the pulmonary system as an RVAD, but there is no evidence that this improves clinical outcomes.
- *Indications:* bridge to transplant/destination therapy in the context of HF.
- *Contraindications:* suspected terminal neurological event, malignancy, and active, or high risk of, bleeding complications.
- *Limitations:* limited availability, patient must be anticoagulated, ↑ risk of arrhythmia, bleeding, and infection.

Transvalvular left ventricular assist devices (Impella™)

- The micro-axial rotary pump is placed across the aortic valve under fluoroscopic guidance via a femoral artery puncture, and is capable of delivering 5L/min blood flow, as shown in Fig. 13.24.
- Directly offloads the LV, ↓ end-systolic volumes, ↑ CO, and will in theory ↑ coronary blood flow and perfusion.
- *Indications:* as with IABP—there are no clear indications for use (as demonstrated by the lack of randomized controlled trial data positively correlating their use with improved survival), but can be inserted at the discretion of the interventionalist.
- *Contraindications:* significant aortic valve disease, LV thrombus, mechanical aortic valve replacement.
- *Limitations:* ↑ risk of bleeding as patients require anticoagulation, LV perforation, tamponade, and arrhythmia.

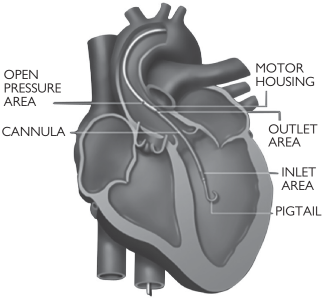

Fig. 13.24 Impella™ device inserted across the aortic valve.

Right heart catheterization and cardiac output assessment

Indications

- Evaluation of cardiac shunts.
- Characterization of valvular disease where TTE/TOE is insufficient.
- Suspected PHT of any cause.
- Prior to heart/lung transplant.

Procedural details

The procedure for undertaking right heart catheterization is outlined in Boxes 13.12 and 13.13.

Box 13.12 Right femoral vein access

- The right femoral vein (RFV) is 0.5–1cm medial to the femoral arterial pulsation.
- The artery is located by palpating below the inguinal ligament.
- The puncture should be slightly lateral to the position of the RFV.
- Vascular ultrasound is recommended to ↓ complications.
- Anaesthetize with a local anaesthetic (e.g. 10mL of 2% lidocaine).
- Warn the patient of pins and needles or transient numbness in the leg—caused by the effects of lidocaine on the femoral nerve.
- A small incision (3–5mm) is made in the skin. The tissue incision may then be dilated by using curved 'mosquito' forceps.
- When venous blood is freely aspirated, pass a 0.035" guidewire into the vein by using a technique similar to that for femoral artery cannulation, and a haemostatic sheath is then introduced.

Box 13.13 Right heart catheterization protocol

- A multipurpose catheter or balloon-tipped catheter may be used.
- Flush the catheter and zero the transducer.
- Advance the catheter to the inferior vena cava and further to the right atrium. Record the phasic and mean pressures.
- Advance into the right ventricle (RV) (see Fig. 13.25).
- Rotation of the catheter and gentle traction will allow the catheter to flick upwards into the RV outflow tract.
- It can then be advanced into the main pulmonary artery (PA) and out to the lung periphery. Occasionally a guidewire is necessary.
- Advance the catheter to the pulmonary capillary wedge pressure (PCWP) position, and record phasic and mean pressures.
- Measure left ventricular (LV) pressures with a pigtail catheter in the LV.
- Check simultaneous PCWP and LV pressure; assess mitral valve gradient.
- Withdraw the catheter slightly; record PA phasic/mean pressure.
- Obtain PaO_2 from the PA (± right and left PAs if patent ductus arteriosus is suspected).
- Withdraw the pulmonary catheter to the RV. Measure and record simultaneous RV and LV pressures.
- Withdraw the catheter to the RA, and measure the pressures again.
- Pull back the LV catheter to the aorta to record any gradient.
- Measure aortic saturations to allow calculation of cardiac output.

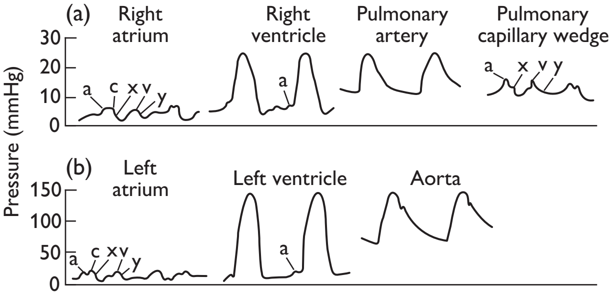

Fig. 13.25 (a) Right heart catheterization pressure waveforms. (b) Left heart catheterization pressure waveforms.

Shunts

To assess shunts, oxygenation must be assessed with samples from the right and left heart. A full saturation run is required (see Box 13.14).

Box 13.14 Shunt oxygen saturation run

- Inferior vena cava
- High superior vena cava
- Mid-superior vena cava
- Low superior vena cava
- Right atrium
- Right ventricle
- Main pulmonary artery
- Right pulmonary artery
- Left pulmonary artery

Cardiac output

- CO is most often measured by using the thermodilution method with a pulmonary flotation catheter.
- CO can also be measured by using the Fick principle, which assesses the difference between the pulmonary arterial and aortic O_2 saturation.

$$\text{Cardiac output } (\text{L}\backslash\text{min}) = \frac{\text{oxygen consumption}(\text{L/min})}{A_oS_aO_2 - PAS_aO_2) \times \text{Hb} \times 1.34}$$

Where Ao = aorta; Hb = haemoglobin; PA = pulmonary artery; SaO_2 = arterial oxygen saturation.

Systemic and pulmonary vascular resistance

- PVR is an important prognostic factor in those with valvular disease, HF, and cor pulmonale.
- Measurement of PVR and SVR is especially important in those being assessed for heart transplantation.
- PVR and SVR are measured in Wood units (mmHg/L/min) or dynes/cm^5, with 80dynes/cm^5 = 1WU.

Cardiac catheterization in valvular heart disease

Valve stenosis

- While echocardiography is the gold standard in assessing valve stenosis, several parameters can be assessed by cardiac catheterization.
- A peak-to-peak gradient can be measured when aortic and LV pressures are recorded during withdrawal of the pigtail catheter across the aortic valve. The gradient is the difference between peak aortic and peak LV pressures (see Fig. 13.26).
- A peak instantaneous gradient is more accurate and measured by using a double-lumen pigtail catheter.
- A mean pressure gradient can be measured by using planimetry of the area of the aortic and LV pressure traces.
- This can be used to calculate the valve area by using the Gorlin equation. A similar method can be used to assess the MV area.

Valve regurgitation

- The severity of AR can be estimated by performing aortography.
- In severe AR, the LV is seen to opacify within one or two beats after contrast injection.
- MR may be assessed by left ventriculography, with contrast seen to opacify the LA and pulmonary veins in severe regurgitation.
- MR may be associated with a prominent 'v' wave on the pulmonary capillary wedge tracing.

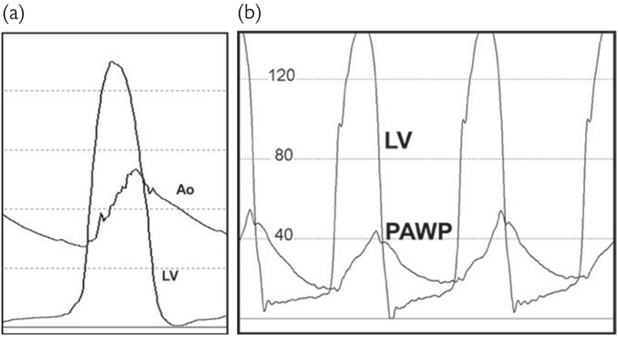

Fig. 13.26 Aortic and left ventricular traces in a patient with aortic stenosis (a) and left ventricular and pulmonary artery wedge pressure traces in a patient with mitral stenosis (b).

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Left atrial appendage closure

- The primary source of thrombus in cardioembolic stroke is the LAA.
- There is significant morbidity associated with stroke.
- Mechanical interventions to close the LAA are especially useful for patients in whom anticoagulation is contraindicated.
- The implant of an LAA occluder is reliant on a trans-septal puncture, and manipulating the LAA itself carries a not-insignificant risk of thrombus embolization.
- Nonetheless, several trials have shown that LAA occlusion may be an effective alternative to PO anticoagulation in some patients.

Indications

- Current ESC guidance suggests that if there is a clear contraindication to conventional PO anticoagulation in patients with AF and a CHA_2DS_2-VASc score of ≥ 2, LAA occluder device implantation can be considered.

Contraindications

- Alternative indication for anticoagulation, active infection, LA thrombus, LA tumour.

Implantation of a left atrial appendage occluder

- The procedure is carried out under local anaesthesia with conscious sedation, or general anaesthesia.
- Both femoral venous and arterial access is gained.
- Access is gained ideally with ultrasound guidance.
- A pigtail catheter is placed at the level of the aortic root to aid in pressure monitoring and assessment of landmarks for trans-septal puncture.
- A trans-septal sheath is inserted over a J-wire to the atrial septum.
- The J-wire is exchanged for a trans-septal needle.
- The needle is used to penetrate the septum, and the sheath is advanced through the septum.
- A guide catheter is then used, over a J-wire, to deploy the device in the left atrial appendage.

Clinical evidence

- Several trials have shown that LAA occlusion may be an effective alternative to PO anticoagulation in some patients.
- The most widely used LAA occluder devices are the Watchman™ (Boston Scientific) and Ampltazer Amulet™ (Abbott) (see Fig. 13.27).
- The Watchman™ device has been assessed against warfarin in the PROTECT-AF trial in patients with AF and a $CHADS_2$ score of ≥ 1, and in the PREVAIL study in patients with AF and a $CHADS_2$ score of ≥ 2. Both of these trials used antiplatelet cross-over in their design; however, the data suggested that these devices were non-inferior to anticoagulation with the end point of stroke.

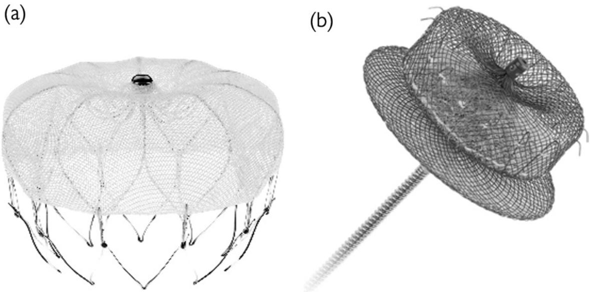

Fig. 13.27 (a) Watchman™ device. (b) Amplatzer Amulet™.

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Complications

- Venous and arterial access complications such as haematoma, pseudoaneurysm, and retroperitoneal bleed (listed in greater detail later in this chapter).
- The most worrying complication is perforation of the atrial free wall, which can occur with the trans-septal needle. This can be catastrophic, and emergency pericardiocentesis is required to prevent circulatory collapse.
- The occluder device can be incompletely deployed, which can result in the LAA remaining partially open. This often requires further LAA manipulation, surgery, insertion of plugs, or anticoagulation.
- Strokes can occur during or shortly after the procedure, owing to manipulation of the LAA and thrombus dislodgement.
- Persistent septal shunts can occur, but these rarely need intervention.

Treatment following left atrial appendage occlusion

- Treatment after closure of the LAA should be tailored to the individual patient.
- Based on data from the PROTECT-AF and PREVAIL trials, patients should take, if possible, full anticoagulation for the first 45 days after closure.
- The patient should then undergo echocardiography (often TOE) to assess patency of the LAA.
- If the LAA is demonstrated to be fully occluded, then DAPT with aspirin and clopidogrel may be taken for 6 months.
- Aspirin may then be taken indefinitely after this.

Patent foramen ovale closure

- PFO is a consequence of a lack of fusion between the septum primum and secundum.
- Associated with migraine headaches and paradoxical embolic strokes (i.e. from right to left).
- Present in ~25% of healthy adults and six times commoner in patients aged <55 years with cryptogenic strokes.

Indications

- Recommended that patients who have cryptogenic stroke undergo investigation for possible PFO with echocardiography.
- PFO closure should be considered if it is believed that the PFO was causative in the stroke (i.e. large enough to facilitate a right-to-left paradoxical embolus), there is a prohibitive risk of recurrence, and the patient has a septal anatomy favourable for closure.

Contraindications

- Large PFO (often >25mm, is considered too large and should be referred for surgical opinion), active infection, LA thrombus, and LA tumour.

Implantation of a patent foramen ovale closure device

- The access site is usually the right femoral vein.
- Echocardiography is used to size the PFO and occluder device (e.g. Amplatzer™ PFO occluder device) (see Fig. 13.28).
- Heparin anticoagulation should be used during the procedure.
- Some operators will insert two large sheaths into the femoral vein—one for access for device delivery and another for drug delivery, temporary pacing wire insertion, or fluid boluses.
- A multipurpose catheter is inserted over a 0.035-inch J-wire.
- The wire is manipulated through the PFO under fluoroscopy guidance. A hydrophilic Terumo™ wire may be used if there is difficulty crossing the septum.
- The occluder device is delivered, and echocardiography is used to assess procedural success.

Clinical evidence

- Several randomized clinical trials have demonstrated that PFO can be associated with cryptogenic stroke, and closure is recommended in some patients.
- The RESPECT (Amplatzer™ PFO occluder device), REDUCE (Gore Helix/Cardiofrom septal occluder), CLOSE, and DEFENSE-PFO (Amplatzer™ PFO occluder) trials demonstrated a significant reduction in the risk of recurrent stroke with PFO closure vs medical therapy.

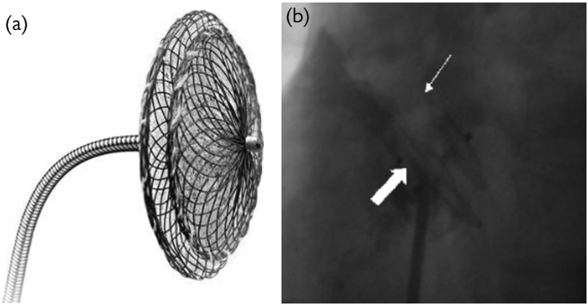

Fig. 13.28 (a) Amplatzer™ occluder device. (b) Fluoroscopic image of Amplatzer™ occluder device with proximal right atrial (large arrow) and distal left atrial (small arrow) sections.

(a) Amplatzer Talisman and Talisman are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, © 2024. All rights reserved. (b) Reproduced from Yang Y *et al*. *American Journal of the Medical Sciences* 2016; **352**(3):245–51 with permission from Elsevier.

Complications

- Venous access complications, such as haematoma and pain, are uncommon if US is used.
- Perforation of the atrial free wall can rarely occur and often mandates emergency pericardiocentesis.
- Incomplete closure of the PFO may result in residual leak and ↑ stroke risk.
- It is rare for patients to experience thromboembolic strokes at the time of PFO closure or shortly after whilst endothelialization of the device occurs.

Treatment following patent foramen ovale closure

- Antiplatelet treatment at around the time of the procedure should be tailored to the individual patient.
- DAPT is usually started pre-procedure with aspirin and clopidogrel. This is continued for between 6 weeks and 6 months after the procedure.
- The patient will have follow-up echocardiography to ensure complete closure of the PFO.
- Aspirin is continued for a minimum of 5 years after the procedure, but often lifelong.

Mitral commissurotomy

- PMC is indicated in patients with symptomatic severe MS and favourable MV anatomy.
- PMC should be carried out by experienced individuals in high-volume centres (example of balloon inflation in PMC shown in Fig. 13.29).
- Surgical intervention is preferred in patients with concomitant significant regurgitation.
- Careful case selection is paramount, as the patient group is often comorbid and the procedure carries not insignificant risk.
- Older patients have poorer outcomes in PMC, related to comorbidity and valve morphology.

Indications

- Patients in whom MV surgery is contraindicated (e.g. extreme age, significant comorbidity) and adequate results can be obtained percutaneously.
- The Wilkins score (grades 1–4) can be used to objectively assess valve morphology (see ➔ Table 4.4).
- The total score ranges from 4 to 16, and a score of <8 predicts favourable outcome with PMC.

Contraindications

- MV area >1.5cm^2.
- LA thrombus.
- Concomitant moderate or severe MR.
- Severe calcification.
- Bi-commissural calcification.
- Other valve or coronary disease that requires cardiac surgery.

Mitral valve commissurotomy protocol

- The access site is usually the right femoral vein.
- A right femoral artery sheath is inserted for assessment of arterial pressures during the procedure.
- A trans-septal puncture is made into the left atrium and the patient is anticoagulated.
- A dedicated balloon is taken to the septum and passed into the left atrium (LA) over a J-wire.
- The balloon should pass into the left ventricle (LV), with a small inflation via blood flow into the LV from the LA.
- The balloon can be passed into the LV with a stylet if it does not passively progress through the mitral valve orifice.
- The distal balloon is inflated and withdrawn, such that contact is made with the LV side of the mitral valve.
- The proximal balloon is then inflated, which results in dilatation of the mitral valve cusps.

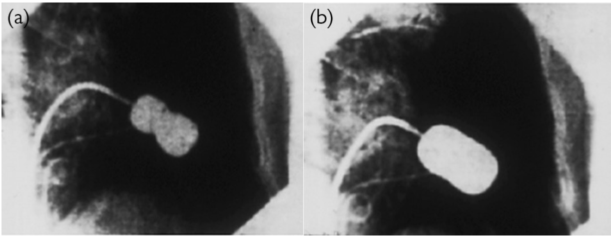

Fig. 13.29 Balloon mitral valvuloplasty. Panel (a) shows the balloon partly inflated across the mitral valve, demonstrating the typical dumbbell shape. As the inflation pressure and volume are i, the stenosed valve dilates (b).

Reproduced from Braunwald E (ed) *Heart Disease: a textbook of cardiovascular medicine*. 5th ed (2001) with permission from Elsevier.

Clinical evidence

- Evidence suggests that short- and medium-term outcomes are comparable between percutaneous valvuloplasty and surgical valve commissurotomy.
- Repeat procedures are required in <50% of the cases that have successful PMC.

Complications

- Vascular access itself is low risk with the assistance of US.
- A trans-septal puncture is associated with perforation of the atrial free wall and residual persistent ASD; however, these are rare.
- Free wall punctures often result in tamponade requiring emergency pericardiocentesis.
- PMC may be unsuccessful, and significant residual stenosis may require further percutaneous intervention or cardiac surgery.
- In calcific MV, the stenosis may progress to significant regurgitation. This may require surgery to replace the valve and patients should be consented for this risk.
- At the time of inflation, patients rarely may experience thromboembolic complications such as stroke.

Treatment following procedure

- No additional medical therapy is indicated following PMC.
- Patients should be anticoagulated with warfarin if they develop AF.
- Patients should be followed up to assess symptoms of restenosis, which usually requires surgical repair/replacement of the valve.

Transcatheter aortic valve implantation

- An ageing population has ↑ the numbers of patients presenting with symptomatic AS.
- The gold standard intervention had been surgical aortic valve replacement (SAVR); however, more patients are having TAVI owing to ↑ safety and centre experience.
- Data now suggest that TAVI is indicated as an alternative to SAVR in some patient groups.

Indications

- Symptomatic severe AS, but too high risk for surgery.
- Favourable anatomy for percutaneous aortic valve implantation, taking into account the aortic root dimensions, vascular tortuosity, access sites, and calcification of the aorta.

Contraindications

- Short (<1 year) life expectancy, regardless of valve implant or not.
- Particularly small/large annulus depending on available prostheses.
- Porcelain aorta.
- Active endocarditis.
- Thrombus within aorta.

Transcatheter aortic valve protocol

- Pre-procedure cardiac CT imaging with estimation of dimensions of the femoral artery, aorta, and aortic root must be carried out to assess anatomy. Patient selection with favourable vascular access, aorta, and root is key to procedural success.
- Requires a cardiac anaesthetist for general anaesthesia or conscious sedation, and an imaging cardiologist to provide TOE/TTE.
- Common to have two interventionalists scrub to implant the valve.
- On-table TOE is required to size and position the valve; however, in the frail or haemodynamically compromised patient where this is not possible, high-quality TTE may be sufficient.
- Arterial and venous access is required for delivery of the device, drugs, and a temporary pacing wire.
- Whilst the preferred access point is the femoral artery, other approaches can be used such as apical, carotid, and subclavian.
- Aortic and coronary angiography to assess size and suitability.
- A delivery sheath is inserted over the femoral artery wire.
- The patient is anticoagulated and the valve is crossed with a straight guidewire and an Amplatz catheter.
- A temporary pacing wire is inserted which paces ~200bpm during balloon inflations and valve deployment.
- The aortic valve is ballooned (aortic valvuloplasty) (see Fig. 13.30).
- The valve prosthesis is positioned and deployed.
- Aortography and coronary angiography are performed to assess for paravalvular leak and the coronary ostia.

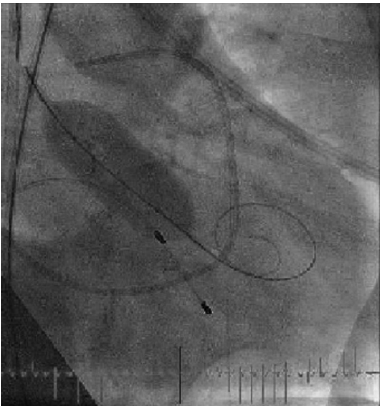

Fig. 13.30 Balloon inflation across the aortic valve.

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Clinical evidence

- The PARTNER randomized clinical trial series (SAPIEN, SAPIEN XT, and SAPIEN 3) have demonstrated that TAVI is safe, with lower composite rates of death, stroke, and readmission at 1 year, in high-, medium-, and possibly even low-risk patients.
- UK TAVI (SAPIEN 3, Evolut/Evolut R, Lotus) has demonstrated that TAVI is non-inferior to SAVR in terms of all-cause mortality, with high transfemoral success rates.

Complications

- Vascular access complications, including bruising, haemorrhage, and retroperitoneal bleeding.
- Tamponade.
- Aortic root rupture.
- Coronary obstruction.
- AR and paravalvular leak.
- CHB.
- Contrast-induced nephropathy.

Treatment following procedure

- Patients can be managed with a single antiplatelet agent after the procedure, which must be continued lifelong.
- Patients with another indication for PO anticoagulation (e.g. AF) should resume this and the risk–benefit of continuing an antiplatelet with anticoagulation needs to be individually assessed.

Common complications of coronary and structural interventions

Complications of coronary interventions

- Diagnostic coronary angiography carries less risk than PCI, as wire manipulation and stent delivery ↑ procedure length, required size of sheaths, plaque disturbance, and coronary injury.
- The complications described below can occur in any invasive coronary procedure.

Radial artery complications

- One of the main advantages of radial access is ↓ complication rates.
- Bleeding can be managed with direct pressure.
- Pseudoaneurysms can form and are diagnosed with US. They often require thrombin injection.

Haematoma and haemorrhage around access site

- The incidence of haematoma formation is related to procedure length, sheath size, use of anticoagulation, and technique of sheath removal.
- Local haematoma can be managed with pressure but can lead to significant blood loss or pseudoaneurysm.
- Femoral artery punctures can result in bleeding into the retroperitoneal space. This presents as haemodynamic collapse and requires CT to confirm the diagnosis. It is often treated with blood products.

Pseudoaneurysm

- A pseudoaneurysm results from rupture of the arterial wall at the puncture site, with the formation of a false aneurysm involving the media and adventitia, and presents as a pulsatile mass.
- Pseudoaneurysms are best visualized with US. Small pseudoaneurysms can often be managed by direct compression. Large pseudoaneurysms may require thrombin injection or surgical intervention.

Acute limb ischaemia

- This is rare and usually occurs in patients with pre-existing limb ischaemia who undergo femoral procedures. It presents as a painful, pale, pulseless, and cold limb.
- If suspected, an urgent review by the vascular surgical team is needed.

Vasovagal reactions

- These are common during angiography at the time of sheath removal and are characterized by hypotension and bradycardia.
- They can be treated with IV fluids and atropine.

Arrhythmia

- Brief episodes of SVT and salvos of VT are common and transient with wire and catheter manipulation.
- VF may occur during contrast injection and should be defibrillated.
- Sustained VT should be treated as per ALS guidelines.

Contrast-related complications

- Rash, urticaria, blurred vision, and rigors are relatively common.
- Symptoms can be treated with 10mg of chlorphenamine and/or 100–200mg of hydrocortisone.
- Anaphylactic reactions are rare, but these should be managed with adrenaline, chlorphenamine, hydrocortisone, and fluids.
- Acute renal injury and contrast-induced nephropathy are common in patients with renal impairment. Patients should be pre-hydrated. The lowest volume of contrast should be used, where possible.

Complications specific to structural interventions

In addition to the complications described above, structural interventions are subject to additional risks as detailed below.

Vascular access complications

- Risks of vascular complications are similar to those of conventional femoral approach in coronary angiography; however, patients are at ↑ risk due to the larger sheaths used to deliver equipment.

Tamponade

- Rare and requires emergency pericardiocentesis. It can occur for a number of reasons; however, it is usually related to wire penetration and perforation.
- This can occur with RV temporary pacing wire insertion, perforation when crossing the aortic valve in TAVI, LA free wall perforation in PFO/ASD closure, or MV interventions.

Aortic root rupture

- Rare and is often fatal. It results from rupture of the root with balloon/valve deployment in TAVI.

Coronary obstruction

- Can occur with TAVI when the valve is deployed directly over the left or right coronary ostia with valve struts or as a result of displacement of the native valve leaflets and/or plaque shift in the aortic root.

Aortic regurgitation

- Occurs in TAVI if the incorrect-sized valve is selected or incompletely inflated. Percutaneous plug devices can be successful in occluding paravalvular leak.

Pacemaker insertion

- Common in TAVI owing to distortion of local conducting tissue in or around the AV node. It is common practice to insert a permanent pacemaker pre-emptively if there is evidence of significant conducting tissue disease (RBBB and complicated LBBB).

Stroke

- Can occur following any structural intervention. Minimized by use of anticoagulation during the procedure.
- The role of cerebral protection devices is still under investigation.

Chapter 14

Invasive electrophysiology and devices

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Mechanism of tachycardias

Knowledge of how arrhythmias are initiated and perpetuated is fundamental to understanding the techniques described in this chapter.

The electrical wavefront

- An excitable impulse is generated at the cell membrane.
- As cells depolarize, it results in a reduction in negativity of the resting potential in adjacent cells, such that they also reach the threshold potential and depolarize.
- The shape, orientation, and presence of gap junctions between myocardial cells allow rapid progression of this depolarization, which can be described as an electrical *wavefront*.
- After a cell has depolarized, it cannot depolarize again until a period of recovery time has passed—the *refractory period*. Cells that are able to depolarize are *excitable*, and those that cannot are *refractory*.
- In SR, the source of these wavefronts is the SAN, and they may be transmitted between the atrium and the ventricle by the AVN. They are initiated (and therefore, the HR is controlled) by regulation from the autonomic nervous system and circulating catecholamines.

Conduction block

- A wavefront will propagate as long as there are adjacent excitable cells.
- *Fixed conduction blocks:* anatomical barriers, such as the MV annulus, vena cava, and aorta, do not contain myocardial cells, and therefore, the progression of wavefronts is halted there. Dead cells are another important source of fixed conduction block (e.g. the LV scar of an MI).
- *Functional conduction block:* describes the situation when the block is only present under certain conditions (see Box 14.1). An example is myocardial ischaemia, which may alter the electrical properties of myocytes, so that they do not conduct. It is also a functional block that prevents a wavefront from turning back on itself, as the cells behind the leading edge are temporarily refractory and force the wavefront to continue in one direction.

Box 14.1 Key causes of functional conduction block

- Myocardial ischaemia
- Cells in a physiological refractory period
- Cyanosis
- Myocardial stretch

Arrhythmia mechanism

Three distinct mechanisms are described:

- Enhanced automaticity
- Re-entry
- Triggered activity.

The first two account for nearly all clinical tachycardias, and their characteristics are compared in Table 14.1.

Table 14.1 Characteristics of automatic and re-entry tachycardias

	Automatic	Re-entry*
Autonomic sensitivity (e.g. to exercise, emotion)?	Often	Unusual
Reproducible induction and termination by programmed pacing?	No	Yes
Entrainment of tachycardia by pacing? (See Box 14.2)	No	Yes
Induced by atropine/ isoprenaline infusion?	Yes	May augment induction by pacing*
Related to metabolic causes	Often	Unusual
Onset/offset	May be gradual (warm up and down)	Sudden
Specific tachycardias caused	Focal atrial tachycardia, RVOT VT	Macro-re-entrant atrial tachycardia, AVNRT, AVRT, VT

[*] The conduction properties of, for example, the atrioventricular node, are influenced by autonomic tone. Spontaneous or drug-induced changes in this may then influence the development of re-entry tachycardias such as atrioventricular re-entrant tachycardia, atrial fibrillation, atrioventricular re-entrant tachycardia, right ventricular outflow tract and ventricular tachycardia.

RVOT, right ventricular outflow tract; VT, ventricular tachycardia; AVNRT, atrioventricular node re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia.

Box 14.2 What is entrainment?

- During an electrophysiology study, tachyarrhythmia is induced, causing the myocardium to repeatedly depolarize.
- To test entrainment, the myocardium is stimulated earlier than would be expected in the arrhythmia.
- If the stimulated myocardium is part of a re-entry circuit, this will depolarize the circuit earlier than normal and the arrhythmia will jump forward (‘reset’).
- If the myocardium is repeatedly stimulated ahead of the depolarization wave, the arrhythmia will repeatedly reset and appear to have a shorter cycle length. This is entrainment.

Mechanism of arrhythmias

Enhanced automaticity

- A nidus of myocardial cells depolarizing faster than the SAN (rapid phase 4 of the action potential) (see Fig. 3.1) will act as the source of wavefronts that conduct through the heart.
- The nidus may be atrial/ventricular. If atrial, it will override the SAN.
- As they occur from a single site, they are often termed *focal*.

See Box 14.3 for common sites for enhanced automaticity.

Box 14.3 Common sites for enhanced automaticity

Common sites are where myocardial cells change shape/size or those under abnormal pressures:

- Right atria/superior vena cava border
- Left atria/pulmonary vein border
- Crista terminalis
- Coronary sinus (CS)
- Koch's triangle (CS, tendon of Todaro, tricuspid valve leaflet)
- Atrioventricular node area
- Mitral/tricuspid ring
- Ventricular outflow tracts

Re-entry

Accounts for >75% of clinical arrhythmias. It is caused by a propagating wavefront that is perpetually meeting excitable myocardium. For re-entry to occur, ≥2 pathways must exist around an area of conduction block. Below is an example of VT due to myocardial scar (see Fig. 14.1).

- A myocardial scar acts as an area of block, around which a wavefront passes via normal myocardium (A) and slowly through it via diseased myocardium (B)—hence there are two distinct pathways.
- The sinus beat (see Fig. 14.1, panel 1) is followed closely by a ventricular ectopic. This is conducted through A normally, but not through B, which is still refractory (see Fig. 14.1, panel 2).
- The distal end of B, however, is now excitable and the wavefront passes backwards up B, which has had time to fully recover by the time it reaches the proximal end (see Fig. 14.1, panel 3). Conduction is sufficiently slow up B that now A is excitable again and the wavefront can pass down A.
- Thus, a wavefront is always meeting excitable myocardium.

Triggered activity

- This has features of both above mechanisms. It is caused by spontaneous (hence automatic) *after-depolarizations* (ADs) occurring late in phase 3 (*early ADs*)/phase 4 (*delayed ADs*) of the action potential.
- ADs are inducible and often triggered by premature beats (like re-entry).

- If these ADs reach the threshold level, then a single, or burst of, action potential is set off. ADs can be induced experimentally by ischaemia, QT-prolonging drugs, cell injury, or low K^+ level.
- This underlies TdP and digoxin toxicity arrhythmias.

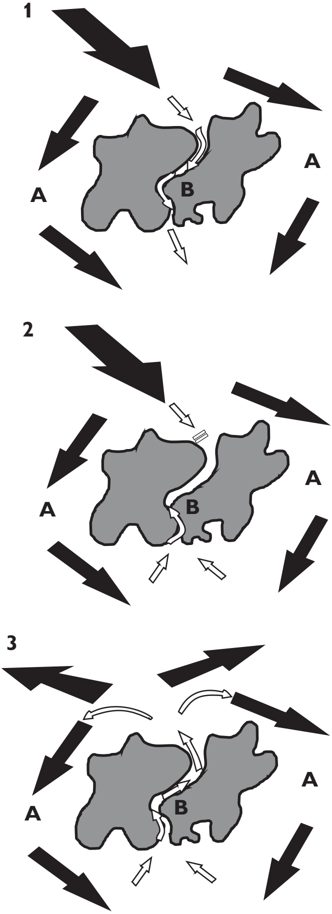

Fig. 14.1 Re-entry as a mechanism of tachycardia. (1) Normal sinus beat passing around and through scar. (2) Ectopic beat passing around, but blocked through scar. (3) Re-entry circuit of tachycardia. (Dark grey represents scar; light grey represents normal myocardium; white arrows represent electrical wavefronts.)

The electrophysiology study

- The EP study is most useful for tachycardia diagnosis.
- When a tachycardia has already been documented or is strongly suspected, then an EP study is usually the first part of a combined procedure with catheter ablation to cure the arrhythmia.

Timing of arrhythmia rates in electrophysiology

- It is usual to discuss cycle length (in milliseconds) rather than the heart rate.
- Cycle length is the time between waves (e.g. the RR interval):
    - 60 beats/min = 1000ms cycle length
    - 100 beats/min = 600ms cycle length
    - 150 beats/min = 400ms cycle length.

Mapping electrical activity in the heart

- EP studies are simply a recording of the heart's electrical activity during SR or arrhythmia, or when pacing at specific sites.
- *ECG:* summates cardiac activation, providing significant information. A 12-lead ECG is recorded throughout.
- *Intracardiac electrogram (ICegram):* by placing 2mm electrodes on the heart's endocardial surface, the electrical activity at precise locations can be ascertained, creating an ICegram. The ICegram is narrower than the ECG and is best appreciated at a sweep speed of 100–200mm/s, four times faster than a standard ECG recording.
- *Electrodes:* the potential difference between two adjacent electrodes (a bipolar electrogram) or one electrode and infinity (a unipolar electrogram) can be recorded. The unipolar electrogram is more accurate regarding the location of electrical activity. However, it is subject to greater interference due to inability to selectively amplify signals.
- *Pacing:* a current can be passed through any of these electrodes to create a pacing stimulus (see Box 14.4).
- *Catheter position:* standard catheter location is shown in Fig. 14.2.

Box 14.4 Pacing in electrophysiology studies

Pacing in the EP study (*programmed stimulation*) has three forms:

- *Incremental pacing:* the pacing interval starts just below the sinus interval and is lowered in 10ms steps until block occurs or a predetermined lower limit (often 300ms) is reached.
- *Extra stimulus pacing:* following a set of 6–10 paced beats at a fixed cycle length ('drive train'), a further paced beat is introduced at a shorter interval (the extra stimulus). Each paced beat of the drive train is termed S_1, the first extra stimulus S_2, any additional extra stimuli S_3, S_4, etc. An extra stimulus can also be introduced after sensed heartbeats ('*sensed extras*').
- *Burst pacing:* pacing at a fixed cycle length for a predetermined time.

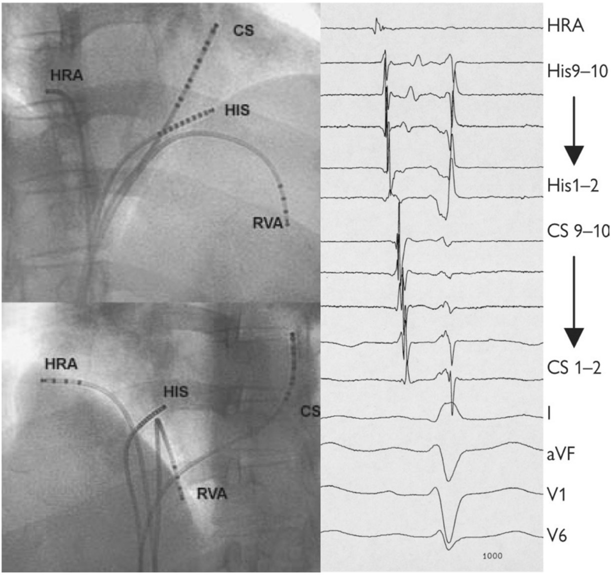

Fig. 14.2 Standard positions of catheters in the electrophysiology study and intracardiac electrograms at those sites. Catheters have been passed up into the right heart from sheaths in the femoral veins under fluoroscopic guidance. These images from the right anterior oblique (above) and left anterior oblique (below) demonstrate the standard positions at the high right atrium (HRA) close to the sinoatrial node, on the His bundle (HIS), at the right ventricular apex (RVA), and a catheter passed through the os of the coronary sinus (CS), which wraps around the left posterior atrioventricular groove. From this position, ICegrams are recorded from the left atrium and ventricle. This catheter is often inserted via the left or right subclavian vein.

ICegrams are conventionally ordered HRA, HIS, CS, and RV (not displayed here), with an ECG lead at the bottom. On each catheter, bipoles are then ordered proximal to distal. In sinus rhythm, then activation is seen to start at the HRA, pass across the His bundle, and then along the CS catheter proximally to distally. The earliest ventricular activation is at the RVA (where the Purkinje fibres insert).

Normal *sinus intervals* are PA 25–55ms, AH 50–105ms, HV 35–55ms, QRS <120ms, and corrected QT <440ms in men and <460ms in women.

Uses of the electrophysiology study

Sinus node function

- The *corrected sinus node recovery time* and *sinoatrial conduction time* are both measures of SAN function.
- Unfortunately, they are unreliable tests. SAN function is significantly influenced by autonomic tone, drugs, and observer error; it is better assessed by ambulatory monitoring and exercise testing.
- EP studies rarely contribute to decisions regarding pacemaker (PPM) treatment for SAN dysfunction and are not routinely done.

Atrioventricular conduction

Heart block

- The degree of heart block is assessed by the ECG, which can also indicate the level of block (i.e. at the AVN or in the His–Purkinje system).
- The level of block is ascertained in the EP study. The atrial–His (AH) time is prolonged in nodal block, and the His–ventricle (HV) time in infranodal block. The AH (but not the HV) time may be ↓ by exercise, isoprenaline, or atropine, and ↑ by vagal manoeuvres.

Atrioventricular nodal function

This is assessed both anterogradely (A to V) and retrogradely (V to A) by using both incremental and extra stimulus pacing.

- *Wenckebach cycle length (WCL):* incremental pacing is initiated at the high RA (HRA); conduction is observed in the His bundle and RV apex (RVA) until block occurs. The longest interval at which block occurs is the anterograde WCL. Normal values are <500ms; however, this ↑ with age and autonomic influences. The retrograde WCL is also measured; however, absent VA conduction can be normal.
- *Effective refractory period (ERP):* extra stimulus pacing is performed from the HRA. As the coupling interval ↓, AV conduction is observed. The longest S_1–S_2 interval when block occurs is the anterograde AVN ERP. If VA conduction is present, the retrograde AVN ERP is measured.

Decremental conduction

This is a key physiological property of the AVN. As the interval between impulses passing through the AVN shortens, the conduction velocity within the AVN also ↓.

- In AV conduction, this is manifest as a prolongation of the AH (and AV) interval, as the atrial pacing interval ↓.
- This can be observed during incremental and extra stimulus pacing. During extra stimulus pacing, the AH interval can be plotted against the S_1–S_2 interval to create an anterograde conduction curve.

Dual atrioventricular nodal physiology

Many patients have two atrial-to-AVN electrical connections; these are the substrate for AVNRT.

- These connections have different properties. The *slow pathway* has a slower conduction velocity, but a shorter ERP than the *fast pathway*.

- These properties are seen on an anterograde conduction curve. At longer A_1–A_2 intervals (gap between two atrial stimuli), conduction is via the fast pathway. Once the fast pathway ERP is reached, conduction is via the slow pathway; the AH time suddenly is prolonged (*AH interval* jump, defined as an ↑ of the AH time by >50ms, following a 10ms A_1–A_2 interval reduction).

Identifying abnormal atrioventricular connections

- *Normal hearts:* there is only one connection between the atrium and the ventricle—the AVN. Activation of the atrium (during V pacing) or ventricle (during A pacing/SR) should start at the AVN.
- *Accessory pathways (APs):* these do not decrement. Their presence can be identified by both abnormal activation patterns and conduction physiology by using incremental and extra stimulus pacing.

Atrial pacing

As the AVN decrements, a greater proportion of ventricular activation will occur via the AP. Thus, non-decremental AV conduction times and broadening of the QRS complex will be observed as the pacing interval shortens. If the ERP of the AP is longer than the ERP of the AVN, then the QRS will suddenly narrow and the AV time is suddenly prolonged when the AP blocks.

Ventricular pacing

The normal order of atrial activation is the His bundle, then the coronary sinus (CS) (proximal to distal), and finally the HRA, termed *concentric* (midline) activation. If the atrium is activating via an AP, an *eccentric* (non-midline) activation pattern is observed. The site of the earliest atrial activation will localize the AP. Non-decremental VA conduction is also seen.

Induction of arrhythmia

- The presence of an AP, dual AVN physiology, or a known ventricular scar provides the substrate for tachycardia but does not necessarily imply it will occur. A diagnosis can only be confirmed by inducing the tachycardia.
- In addition to the techniques described, burst pacing, extra stimulus pacing with multiple extra stimuli, and sensed extras are deployed.
- If this fails, pacing manoeuvres can be repeated during an isoprenaline infusion (1–4mcg/min) or boluses (1–3mcg). This is particularly important for tachycardias due to enhanced automaticity.
- 'Aggressive' induction protocols ↑ the likelihood of inducing an unwanted arrhythmia such as AF or VF.
- Once tachycardia is initiated, it is useful to compare it with a 12-lead ECG recorded during symptoms, to ensure this is the clinical arrhythmia (see ➔ Tachyarrhythmias: classification, p. 142 for details on how individual tachycardias are diagnosed and treated).

Table 14.2 A standard basic electrophysiology study

Pacing protocol	Measure	Comments
1. Sinus rhythm	Basic sinus intervals (PA, AH, HV, QRS, QTc)	Is there AV conduction block?
2. Incremental ventricular pacing	Retrograde WCL	Is VA conduction present? If so, is atrial activation normal and decremental?
3. Incremental atrial pacing	Anterograde WCL	Is AV conduction decremental? Is pre-excitation manifested?
4. Extra stimulus pacing from atrium at 600 and 400ms	Anterograde AVNERP at 600 and 400ms	Is AV conduction decremental? Is pre-excitation manifested? Is there dual AVN physiology?
5. Extra stimulus pacing from ventricle at 600 and 400ms	Retrograde AVNERP at 600 and 400ms	Is VA conduction present? If so, is atrial activation normal and decremental?
6. Arrhythmia induction from atrium. Use 2–4 extra stimuli, sensed extra stimuli, and burst pacing		Note pacing protocol that induces arrhythmia. Is it reproducible? Compare with clinical arrhythmia
7. If VT is suspected, perform the Wellen's protocol	VERP at 600 and 400ms	
8. Repeat steps 2–7 during isoprenaline infusion		Essential in enhanced automaticity tachycardias

AV, atrioventricular; WCL, Wenckebach cycle length; AVNERP, atrioventricular node effective refractory period; AVN, atrioventricular node; VT, ventricular tachycardia; VERP, ventricular effective refractory period.

Indications for electrophysiology study

- To diagnose the mechanism of documented symptomatic tachycardia (usually proceed immediately to ablation)
- To diagnose the mechanism of tachycardia in a patient with palpitations and suspected arrhythmia (may proceed immediately to ablation)
- To determine the electrical properties of an accessory pathway (Wolff–Parkinson–White)—to stratify the risk of sudden cardiac death and the need for ablation
- To diagnose the mechanism of syncope—when arrhythmia is strongly suspected (e.g. bifascicular block)*
- To look for evidence of atrioventricular nodal conduction disease and the need for permanent pacemaker*

* Rarely performed in modern practice.

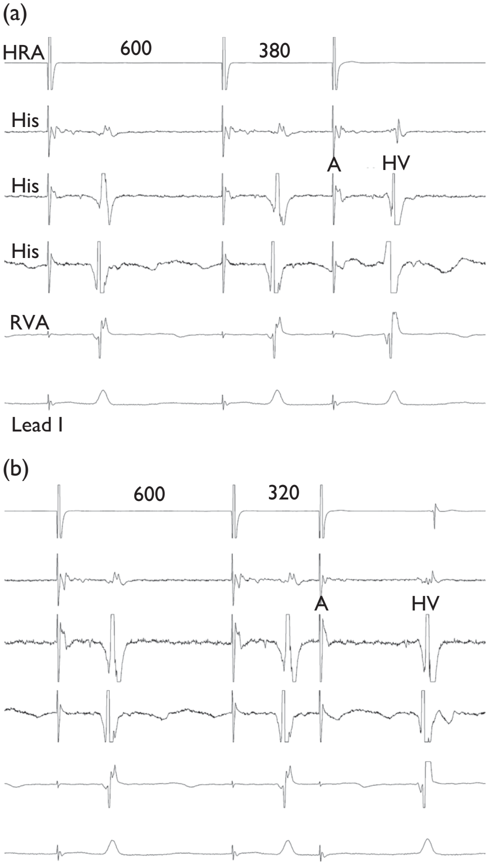

Fig. 14.3 AV nodal jump demonstrated during anterograde conduction curve. In both panels, five ICegrams are shown; top to bottom: high right atrium (HRA), three bipolar recordings from the bundle of His (His), right ventricular apex (RVA) and lead I of the ECG are displayed. Eight paced beats (drive train) have been delivered through the HRA at 600ms, and then a single extra stimulus. Only the final two beats of the drive train and the extra stimulus are shown. The coupling interval of the extra stimulus is 380ms and 320ms in panels (a) and (b), respectively. Despite only a slight shortening of the coupling interval, there is dramatic lengthening of the AH (and AV) time, suggesting dual atrioventricular nodal physiology.

Programmed ventricular stimulation

An EP study focusing on induction of ventricular arrhythmias (the VT stimulation study) has previously been used to risk-stratify for SCD, and to decide on the effectiveness of AADs in suppressing VT and the need for an ICD.

Evidence has now accumulated, however, that it is of little predictive value and that decisions regarding ICD prescription should be based on other risk factors, particularly LV function.

The EP study can be useful prior to ICD implant for other reasons:

- To aid in programming of the device:
  - Is VT well tolerated haemodynamically?
  - Is it easily terminated with overdrive pacing?
  - Is there VA conduction? During V pacing or VT?
- To assess suitability for VT ablation (e.g. bundle branch VT)
- To assess for the presence of other arrhythmias and whether they are easily induced.

Programmed ventricular stimulation protocol

- Programmed ventricular stimulation is performed by using the protocol devised by Zehender *et al*., or a modification thereof (see Box 14.5).
- The pacing protocol becomes gradually more aggressive.
- The more aggressive the induction protocol, the less specific the result.
- The most useful result is induction of sustained monomorphic VT with one or two extra stimuli.
- This indicates a potential substrate for ventricular arrhythmias. NSVT, polymorphic VT, and VF are all non-specific results.

Box 14.5 Programmed ventricular stimulation

- From the right ventricular apex extra stimulus pacing, reduce the coupling interval until refractory:
  - One extra stimulus during sinus rhythm
  - Two extra stimuli during sinus rhythm
  - One extra stimulus following eight paced beats at 600ms
  - Two extra stimuli following eight paced beats at 600ms
  - One extra stimulus following eight paced beats at 400ms
  - Two extra stimuli following eight paced beats at 400ms
  - Three extra stimuli during sinus rhythm
  - Three extra stimuli following eight paced beats at 600ms
  - Three extra stimuli following eight paced beats at 400ms
- If no ventricular arrhythmia is induced, repeat from right ventricular outflow tract.

Additional technologies

Non-fluoroscopic three-dimensional mapping

- EP procedures have become increasingly complex (e.g. ablation of AF or AT in CHD), leading to longer procedures with greater X-ray exposure.
- Electroanatomical mapping systems help to overcome these challenges by generating a 3D image as the ablation catheter is moved around the cardiac chamber being mapped.
- Three commonly used systems include: *CARTO*™ (Biosense Webster) and *NavX*™ (St Jude Medical), which locate the catheters by using magnetic and electrical fields, respectively, and *RHYTHMIA*™, which uses both magnetic and impedance-based techniques.
- These maps are used as anatomical guides and can display the timings (activation maps) or voltages of ICegrams represented by colours. The maps can be viewed in any orientation or from internally.
- Points of interest or labels (e.g. ablation lesions) can be marked. This is useful in AF ablation where a series of ablation points need to be delivered to form continuous circular or linear ablation lines.
- Identification of areas of scar (voltage mapping) is essential in VT ablation, as these are critical to its re-entrant mechanism.
- *Non-contact mapping* (Ensite Array, St Jude Medical) allows simultaneous collection of ICegrams from the endocardial surface of the chamber in which the catheter is placed. An array of 64 unipolar electrodes, mounted on a balloon, record the signals from the endocardium conducted through the blood. These signals are reconstructed and displayed on a map of the chamber.

Image integration

(See Fig. 14.4)

- A CT or MRI scan of the patient's thorax can be segmented to provide a 3D image of the patient's own LA (or other chamber).
- This is then registered with the mapping system by moving the mapping catheter to anatomical points (e.g. junction of a pulmonary vein and the LA) and simultaneously marking them on the image and mapping system.
- The reconstruction of the LA is then locked into the mapping system, so that the operator can navigate around the complex unique anatomy of a patient's LA without the need for X-ray.

Remote navigation of ablation catheters

- Robotic technologies have been a great success in urological and cardiac surgery. In order to overcome difficulties with manual catheter manipulation in complex procedures, these have been applied in EP—with the operator seated in the laboratory control room rather than standing by the patient.
- Proposed advantages are: improved catheter stability and reach, better ablation lesion formation, and reduced operator X-ray exposure and fatigue.
- Two commonly used systems exist: *Niobe*® (magnetic driven, Sterotaxis) and *CARTO*™.

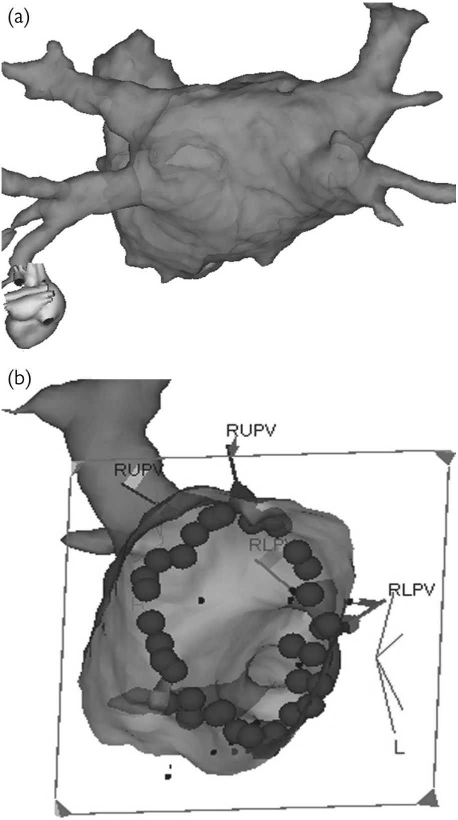

Fig. 14.4 Image integration. (a) The left atrium from the posterior–anterior perspective reconstructed from a magnetic resonance scan of the heart taken pre-procedure. The image is registered with the three-dimensional mapping system. (b) The left atrium viewed from within at a left lateral projection, so that the ablation lesions that have been delivered around the right pulmonary veins are visible.

Catheter ablation: energy sources

- In medical terms, ablation is removal of tissue.
- As most tachycardias depend on discrete foci or pathways to be sustained, they are amenable to cure by destruction of these areas.

Radiofrequency energy

- The most common form of ablation energy currently used.
- The radiofrequency (RF) generator delivers an alternating current of 500–1000kHz between the active catheter unipolar platinum–iridium electrode and a large indifferent electrode/patch placed on the patient's skin.
- The RF current causes ions within cells immediately adjacent to the catheter to agitate and generate heat (resistive heating).
- The heat generated is proportional to the current density, which is only high in the immediate vicinity of the catheter tip–tissue interface. As such, significant heating only occurs in this area.
- A lesion of ~5mm depth is formed after 30–60s, which is sufficient to destroy the full thickness of the atrial myocardium.
- Catheters are 7Fr, with tip electrodes of 4mm in length as standard or 8mm where longer lesions are needed.
- Cells are destroyed by heating to >50°C (see Box 14.6).

Box 14.6 Overheating

- If the temperature approaches 100°C, boiling of cell water occurs, generating steam.
- The steam escapes by exploding either through the endocardium causing a large lesion (cavitation) or through the pericardium (perforation ± tamponade).
- Temperature is monitored at the tip of the catheter, and power delivery is automatically limited to prevent such overheating.
- The generator allows the power, temperature, and duration of each RF delivery to be adjusted.

Irrigated radiofrequency

- The tip of the catheter is cooled during RF by the flow of blood, so the hottest part of an RF lesion is 1mm beneath the surface.
- Stasis of blood flow occurs as the lesion is formed; hence, the temperature ↑, limiting the amount of energy that is delivered, and therefore the size of the lesion (see Box 14.6).
- Heparinized saline, passed through a lumen in the tip of the catheter at a rate of 10–30mL/h, continuously cools the catheter, allowing higher powers and larger lesions to be formed.
- Irrigation is needed where the myocardium is thick (e.g. the LV (VT) or the Eustachian ridge (typical AFl)).
- Low-flow (2mL/h) irrigation is useful to keep the tip of the catheter free of thrombus, reducing stroke risk during RF in the LA or LV.

Cryoablation

- Contained within specialized ablation catheters, liquid nitrous oxide (N_2O) released into the tip rapidly expands/vaporizes and cools (Joule–Thomson effect), removing heat from the tissue in contact with the catheter.
- The gas is rapidly recycled back to the catheter console.
- The tissue temperature (monitored at the tip of the catheter) falls to −30°C, at which stage there is reversible loss of cell function.
- If an appropriate response is seen (e.g. loss of pre-excitation during AP ablation), then the tissue is further cooled to −70°C for 4min to cause permanent destruction.
- Ice forms and adheres the catheter to the tissue, increasing stability.
- If an adverse change is seen (e.g. AVN block) at −30°C, then the tissue can be rewarmed, theoretically without permanent damage.
- Can be used with a balloon catheter (cyroballon) for AF ablation.
- This technique is limited by the depth of lesion that can be created, so it is generally not used for ventricular ablation.

Microwave energy

- Energy is generated through an alternating current at 500–100MHz.
- Tissue temperature is ↑ through dielectric heating of water molecules.
- Cardiac muscle has a greater water content, which leads to ↑ heating, compared with endocardial tissue.
- Theoretically, this allows for a greater depth of heating.

Laser energy

- Lasers produce a monochromatic beam of light at a specific wavelength.
- Laser energy can be precisely directed and modulated to provide excellent control over energy delivery.
- Heating occurs by the photothermal effect where photonic energy is absorbed, leading to excitation of molecules in the tissue.
- Laser energy can create deep lesions, with less thermal diffusion.
- Laser balloons are available for AF ablation.

Catheter ablation: complications

The general complications associated with ablation are described here. The overall major complication rate for ablation of SVT is <1%, and for complex arrhythmia (AF, VT) 3%. Specific issues in AF ablation are discussed later.

Major complications

- *Death* (<0.1%): rare complication, but should always be consented for in ablation procedures.
- *Bleeding:* generally only venous access is used, so major vascular damage requiring surgery is rare. Bleeding may be exacerbated by procedural use of anticoagulation. Haematomas can be due to persistent arterial/venous bleeding, arteriovenous fistula, or pseudoaneurysm. Large local or retroperitoneal haematoma may require transfusion. Compression and reversal of anticoagulation with protamine, recombinant factor VIII (or FFP), vitamin K, or DOAC reversal agents may be necessary. US and contrast CT (CT angio) are used to establish the cause and extent of bleeding.
- *Stroke* (<0.2% for SVT): risk ↑ for left-sided procedures or where cardioversion to SR from AF or AFl occurs (see Box 14.7 for techniques to reduce procedural risk).

Box 14.7 Minimizing stroke risk in ablation procedures

- Preoperative transoesophageal echocardiography to examine for thrombus in the left atrial appendage
- Intraoperative heparin guided by activated clotting time
- Post-operative anticoagulation (vitamin K antagonist or non-vitamin K antagonist oral anticoagulant)
- Use of irrigated catheters
- Continuous pressured heparinized saline administration through left-sided sheaths
- Use of cryoablation

- *Cardiac tamponade* (<0.2% for SVT, ~1% for AF): the risk is higher if trans-septal puncture is performed but can occur even during diagnostic procedures. BP is monitored throughout the procedure and in any hypotensive episode when tamponade is suspected. The EP lab should be equipped with a handheld echo machine and emergency pericardial aspiration sets. Doctors performing trans-septal punctures need to be experts in pericardial aspiration.
- *AV nodal block* (<1% for SVT): high risk of septal AP or AVNRT (slow pathway) ablation. During RF, continuously image the catheter position and atrial and ventricular electrograms. If AV or VA block, or catheter movement occurs, **STOP**. Cryoablation may be preferred for high-risk cases.
- *DVT and PE:* due to placement of multiple catheters in small veins for prolonged periods. If the patient has a tendency to thrombosis, use heparin and continuous irrigation of sheaths.

- *Coronary artery spasm/MI:* transient ST-segment elevation and chest pain may occur without any long-term effect due to spasm.
- *Pneumothorax:* only if a subclavian approach is used for catheters (CS).
- *Ionizing radiation exposure:* EP cases may be prolonged. Deterministic effects, such as skin damage, can be avoided with care to fluoroscopy technique. Women should be counselled and have pregnancy tests if necessary. Non-fluoroscopic catheter location techniques (CARTO™, NavX™) are increasingly being used to help reduce ionizing radiation exposure.
- *Anaesthetic complication:* aspiration and other general complications relating to anaesthesia should be considered. Their frequency will depend on the sedation/anaesthetic regimen used (see Box 14.8).

Box 14.8 Anaesthetic use in catheter ablation

- Most simple electrophysiology studies/ablation procedures can be done under local anaesthesia.
- Use of general anaesthetic is patient- and operator-dependent.
- Complex ablations may require general anaesthesia. However, in some cases, a general anaesthetic may make arrhythmias harder to induce and less stable.

Minor complications

These are common. Liberal use of local anaesthetic and conscious sedation (combined opiates and benzodiazepines administered IV) can prevent these.

- *Chest pain:* occurs transiently during energy delivery; analgesia should be given pre-procedure and as needed throughout.
- *Vasovagal episodes:* can occur during initial percutaneous sheath insertion; ensure the patient has IV access before entering the lab.
- *Groin pain, bruising, or haematoma:* common at puncture site, particularly if anticoagulation is used.

General patient preparation pre-procedure

- Some patients may be required to stop antiarrhythmic agents prior to the procedure. This will depend on the patient and procedure.
- In general, antiarrhythmics may be stopped for SVTs but may often be continued for ventricular arrhythmias.
- Similarly, the period over which patients will need to be 'nil by mouth' will depend on the sedation being used.
- If in doubt, discuss with the person undertaking the ablation procedure.

Trans-septal puncture

- This permits a direct route to the LA via the intra-atrial septum and systemic venous system.
- Previously, the technique was used infrequently by cardiologists for mitral valvuloplasty; however, due to the massive expansion in ablation of AF, it is now a routine skill of the modern cardiac electrophysiologist.
- A detailed description of the technique is available.[1]

Electrophysiology (catheter ablation) indications

- Atrial fibrillation
- Left atrial tachycardia
- Ventricular tachycardia
- Left-sided accessory pathways.

Other indications

- Percutaneous mitral commissurotomy
- Mitral valve repair/replacement
- Insertion of a left atrial appendage occlusion device
- Haemodynamic study of the left heart with prosthetic aortic valve present

Technique

(See Fig. 14.5)

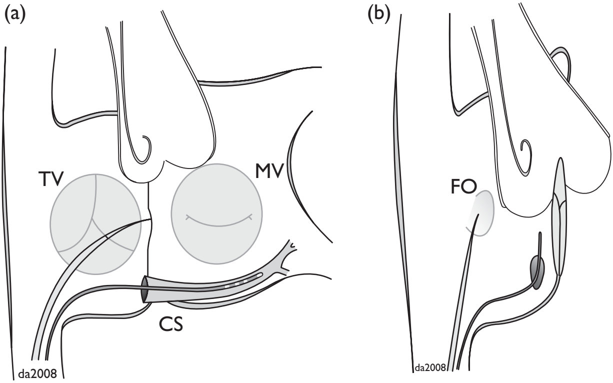

Fig. 14.5 A diagram showing the position of the trans-septal needle optimally positioned in the fossa ovalis (FO) ready for puncture through into the left atrium: (a) left anterior oblique projection; (b) right anterior oblique projection. The most important structure to avoid is the aortic root, in which a pigtail catheter can be sited to visualize it. Alternatively, a catheter marking the os of the coronary sinus (CS) or the bundle of His (not shown) can be used. TV, tricuspid valve; MV, mitral valve.

- *Preparation:* if TOE is performed, review the anatomy of the RA, LA, and intra-atrial septum. Optimal patient preparation—fasted, but well hydrated, with IV access.
- *Percutaneous access:* access is obtained by using the Seldinger technique via the femoral vein. The trans-septal sheaths and dilator are advanced to the SVC over a long guidewire. The needle has a lumen to allow pressure monitoring. The needle is passed up the dilator, but kept just within the tip of the sheath. A catheter is positioned on the His or in the CS, as an anatomical marker.
- *Trans-septal puncture:* the needle and sheath are held together, with the handle pointing towards 4 o'clock. The entire rig is pulled inferiorly while screening in the LAO projection, until the tip of the catheter and needle are seen to 'jump' medially as it falls from the SVC to the RA, followed by a more subtle jump as it falls into the fossa ovalis. The position is confirmed by using the RAO projection to ensure it is posterior to the aortic root. The needle is then advanced through the septum to the LA. The pressure wave changes to an LA trace. The dilator and sheath are advanced over the needle into the LA.
- *Monitoring:* the dilator and needle are removed to leave the sheath in the LA as access for EP catheters. Pressurized heparin saline flush is attached to the sheath. Heparin is given in boluses to keep the activated clotting time (ACT) >300s, while the catheters are in the left heart.
- *RF needles:* these needles use RF energy, rather than mechanical force, to assist in crossing the septum.

Complications

Occur in <1% of cases:

- Pericardial effusion or tamponade
- Aortic root needle puncture
- RA or LA wall needle puncture
- Pleuritic chest pain
- CVA/TIA
- Transient ST-segment elevation of inferior leads
- Persistence of ASD.

Reference

1. Vahanian A, Brochet E. Transseptal puncture for structural heart intervention: an old technique with new indications. *Heart*. 2017;**103**(22):1830–7.

Atrial tachyarrhythmias: mechanism

- There are only two main types of atrial arrhythmias: AT (divided into focal and macro re-entrant forms) and AF.
- *AT:* characterized by repetitive single electrical wavefronts following the same course, causing regular atrial activation. The source can be either focal or a re-entry circuit.
- *AF:* characterized by multiple wavefronts following chaotic, constantly varying courses.

Focal atrial tachycardia

- Atrial cells with enhanced automaticity fire more quickly than the SAN. Any cells can do this (see Box 14.3 for common sites).
- It is possible for re-entrant circuits to form within a very small group of cells, termed 'micro-re-entrant'; however, distinguishing this from a focal mechanism is very difficult, even at EP study.

Macro-re-entrant atrial tachycardia (atrial flutter)

- This is due to a re-entrant circuit bordered by areas of fixed conduction block—either anatomical barriers (e.g. valve annulus) or areas of scar.
- *Typical AFl:* the commonest form of macro-re-entrant AT. The circuit is contained within the RA, rotating anticlockwise around the TV (see Fig. 14.6).

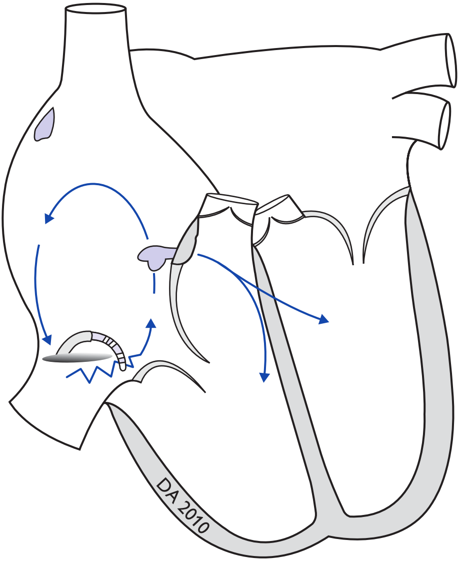

Fig. 14.6 Ablation of typical atrial flutter. The arrows represent the re-entry circuit activating around the right atrium, with the critical isthmus of slowed conduction (zigzag arrow) between the inferior vena cava (IVC) and tricuspid valve (TV) An ablation catheter is passed up from the IVC, and a series of ablation lesions delivered to join the TV to the IVC with a line of scar. In this way, no activation can pass through and the re-entry circuit of typical atrial flutter is broken.

- *Reverse typical flutter:* the circuit rotates in a clockwise direction.
- *Atypical AFl:* any other macro-re-entrant AT in the RA or LA. Most atypical circuits are around areas of scar, most commonly due to catheter ablation of AF, cardiac surgery, or CHD.
- Circuits need to be carefully mapped before ablation is performed.
- The term *flutter* is an ECG diagnosis (i.e. P wave rate >240/min).

Atrial fibrillation

- The mechanism underlying the chaotic electrical wavefronts that characterize AF is both focal and re-entry.

Focal

- Wavefronts emerge from either cells of enhanced automaticity (like focal AT (FAT)) or a small re-entry circuit (micro-re-entrant).
- The pulmonary veins are the wavefront source in >80% of cases.
- The wavefronts are of very high frequency, and the atrial myocardium cannot conduct them uniformly. This causes them to break up to give multiple wavefronts (= fibrillatory conduction) (see Fig. 14.7).
- This is usually the mechanism of paroxysmal AF and these foci are considered triggers of AF.

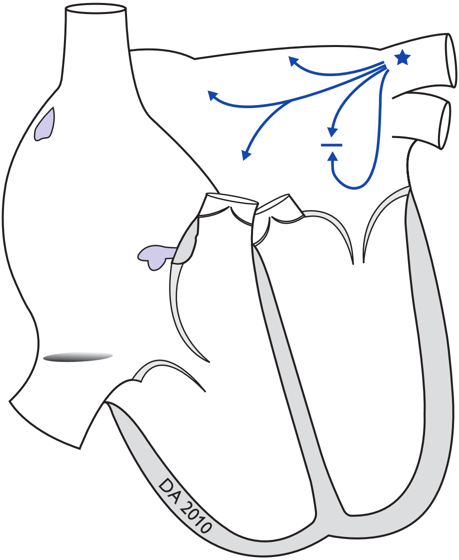

Fig. 14.7 Diagram depicting atrial fibrillation being driven by the source of electrical wavefronts emerging from the left superior pulmonary vein (star). The arrows represent electrical wavefronts breaking up to give multiple wavefronts—the hallmark of atrial fibrillation. Electrical isolation of this vein by ablation will prevent future episodes.

Multiple re-entry

- Four to six separate, self-perpetuating re-entry circuits of constantly varying course and velocity rotate around the atria, colliding with each other and with anatomical structures such as veins and valves.
- The larger the atria, the more room these wavefronts have to rotate and the more likely it is that they will be sustained.

Remodelling

- This is a key concept in understanding the mechanism of AF.
- Episodes of AF, no matter how short, will alter the electrical properties of the myocytes due to downregulation of calcium channels and shortening of action potential duration (electrical remodelling). This makes it easier for the myocardium to support re-entry wavefronts.
- Thus, after multiple paroxysms, AF may become persistent.
- After months of AF, the atria will become dilated and fibrosis will occur (structural remodelling), further promoting re-entry. Remodelling explains the untreated natural history of AF (paroxysmal→persistent→permanent) and the phrase 'AF begets AF'.

Atrial tachyarrhythmias: ablation

Focal atrial tachycardia

- Tachycardia must be induced and sustained to map the location in the atria of earliest activation (the focus), and this may need an isoprenaline infusion.
- The hallmark of FAT is dissociation of atrial from ventricular electrograms during tachycardia. This may occur spontaneously (AV block). It may be necessary to pace the ventricle more than the atrium to demonstrate ongoing atrial activity is not affected by the pacing (cf. AVRT/AVNRT).
- ECG P wave morphology can help to identify the focus (see Box 14.9).
- RA and CS catheters will identify if the LA or RA activates first.
- The RA is easily mapped with an ablation catheter via the IVC, but the LA requires a trans-septal puncture.
- The location of the focus usually has a local electrogram of ≥30ms ahead of the P wave.
- Success rates are >90%.

Box 14.9 P wave morphology and location of atrial tachycardia focus

- +ve leads I and aVL, −ve lead V1 = high lateral RA
- −ve leads II, III, and aVF = LA or RA posteroseptal
- +ve leads I, aVL, and V1 = right pulmonary veins
- −ve leads I and avL, +ve lead V1 = left pulmonary veins

Detailed algorithms are available.[1]

Typical atrial flutter

- The re-entry circuit is interrupted by creating a series of ablation lesions adjacent to one another, so that a line of conduction block is created between the IVC and the TV (see Fig. 14.6).
- This is a purely anatomical procedure; it can be performed in SR or tachycardia.
- Patients in AFl will need peri-procedural anticoagulation with warfarin or a DOAC.
- Commonly, the TV annulus is mapped with a 20-pole catheter, but this is not necessary.
- Success is proved by termination of tachycardia (if present) *and* by demonstrating conduction block in both directions across the RA isthmus (bidirectional block).
- Acute success occurs in 90% of cases, with 10% relapse.
- Thirty per cent of patients who undergo AFl ablation later develop AF.

Reference

1. Kistler PM, Roberts-Thomson KC, Haqqani HM, *et al*. P-wave morphology in focal atrial tachycardia: development of an algorithm to predict the anatomic site of origin. *J Am Coll Cardiol*. 2006;**48**:1010–17.

Catheter ablation of atrial fibrillation

- For paroxysmal AF, the strategy is to electrically isolate the pulmonary vein to prevent episode triggering.
- Ablation of persistent AF starts with pulmonary vein isolation and is followed by further ablation in the LA and RA, aimed at modifying the atria, so that it cannot support the re-entry waves that sustain AF.
- High-volume EP units expect a success rate of 70–90% for paroxysmal AF, although multiple procedures may be required to achieve success.

Indications

- Symptomatic AF despite AADs (ESC Class I recommendation).
- Symptomatic AF as a first-line therapy in selected patients (ESC Class IIa recommendation).
- In patients with symptomatic AF and HFrEF to improve symptoms and cardiac function (ESC Class IIa recommendation).
- To avoid AF-related bradycardia in patients who would otherwise require a pacemaker (ESC Class IIa recommendation).

Patient preparation

- Patients need to be counselled of the 3% risk of a major complication, long procedure time (up to 4h), and the potential need for multiple procedures.
- All patients should have oral anticoagulation for at least 8 weeks after ablation (ESC Class IIa recommendation) or lifelong if indicated by CHA_2DS_2-VASc score (ESC Class IIa recommendation).
- TOE is often performed to confirm the LA and LAA are free of thrombus and to view the intra-atrial septum.
- CT or MRI of the thorax may be performed to provide LA reconstruction for image integration.
- A 3D mapping system may be used (see ➔ Non-fluoroscopic three-dimensional mapping, p. 646). The procedure may be performed under either general or local anaesthesia, with conscious sedation with a combination of opiates and benzodiazepines.
- Percutaneous access is via the femoral veins.
- Heparin is administered to maintain an ACT of 300–400s.

Pulmonary vein isolation

- Trans-septal punctures are performed to deliver an irrigated RF ablation and a circular pulmonary vein mapping catheter to the LA, or other equipment such as a cryoballoon or laser balloon.
- There are multiple methods for isolating the pulmonary veins by using RF energy or cryothermy. Regardless of the technique, the end point is that the pulmonary veins become electrically isolated from the atria.
- It is also possible to isolate the SVC and CS if there are triggers of AF present here.

Substrate modification

- Multiple strategies are adopted to achieve this.
- A *catheter maze* is when the LA and RA are compartmentalized by creating long lines of ablation within them to interrupt the multiple re-entry circuits (see Box 14.10 for common lines used in ablation).

Box 14.10 Common atrial lines in atrial fibrillation ablation

- Left atrial roof (from the left to the right superior pulmonary vein)
- Mitral isthmus (left inferior pulmonary vein to the mitral valve annulus)
- Coronary sinus roof (left atrial septum to left inferior pulmonary vein along the posterior mitral valve annulus)
- Intercaval (superior to inferior vena cava along the lateral right atrium)
- Right atrial isthmus (tricuspid valve to inferior vena cava)
- Within the coronary sinus

- In addition, *complex and fractionated atrial electrograms* (*CFAEs*) are ablated. These signals have high-frequency components and little isoelectric baseline. Several hypotheses exist as to their genesis. Regardless of their cause, their ablation slows and terminates AF.
- AF may organize into regular *AT*. This is usually a macro-re-entrant mechanism, and the circuit is defined by activation mapping with a 3D system and entrainment. Ablation is delivered to interrupt this. A common circuit runs around the MV and can be interrupted by a line of ablation between the MV and the left inferior pulmonary vein.
- If SR is not restored by ablation alone, electrical cardioversion is performed.
- A final check is made of pulmonary vein isolation and of the integrity of lines of block created.

Atrioventricular nodal ablation in atrial fibrillation

- In some individuals, ablation with a curative intent may not be feasible or sensible.
- However, if rate control is difficult or the patient has tachy-brady syndrome, ablation of the atrioventricular node with implantation of an VVI permanent pacemaker may be appropriate.
- A permanent pacemaker is implanted.
- After ~6 weeks, once the pacemaker is well bedded in, the atrioventricular node is ablated, creating iatrogenic complete heart block.
- This allows complete control of the ventricular rate.

Complications of atrial fibrillation ablation

The risk exceeds that of standard SVT, with immediate procedural major complications occurring in 3%.

- *Death*: occurs in <0.2% of all cases, but patients should be made aware of this risk.
- *Bleeding:* groin complications are higher risk due to procedural use of anticoagulation.
- *Stroke/TIA* (<1%): risk higher due to extensive ablation in the LA. Asymptomatic cerebral embolisms occur in 5–20% of cases.
- *Cardiac tamponade* (2%): the most frequent major problem due to a hole created during ablation. Small pericardial effusions may need no treatment, but tamponade requires pericardiocentesis and reversal of anticoagulation. Echocardiography is mandatory if there is any episode of hypotension in the post-operative period.
- *Pulmonary vein stenosis:* this is now unusual (<1%), as ablation is performed at the atrial aspect of the pulmonary vein. To give symptoms, ≥1 pulmonary vein needs to be severely narrowed (>75%) or occluded. It presents insidiously with progressive dyspnoea, fatigue, cough, haemoptysis, and recurrent chest infections. Investigate by contrast CT, MRI, and/or V/Q scan. Angioplasty can be performed.
- *Atrio-oesophageal fistula:* a rare (<0.5%), but usually fatal, complication caused by ablation through the posterior LA. Caution should be taken when ablating in this area (low power, short RF times).
- *Phrenic nerve palsy:* the course of the right phrenic nerve makes it vulnerable to damage during ablation of the lateral RA or right pulmonary veins. Paralysis of the right hemidiaphragm can occur; however, there is almost always full recovery within a few months, with long-term problems being unusual (1–2% of ablations).
- *AT:* occurs in 10–40% of patients within 3 months; persistent > paroxysmal. This may cause much worse symptoms than AF, as the ventricular rate is faster and more difficult to control. Cardioversion, AADs, and AV nodal-blocking drugs can be used, but further ablation is often needed.

Atrioventricular re-entry tachycardias: mechanism

- In young patients with paroxysmal regular narrow complex tachycardia, the diagnosis is either AVNRT or AVRT.
- The mechanism of both is re-entry (see Fig. 14.11).
- The substrate for AVNRT is dual AVN pathways, and for AVRT the presence of an AP.
- Occasionally, a FAT may give an identical ECG appearance.

Diagnostic testing

- Up to four standard catheters are positioned (see Fig. 14.2), and an EP study carried out (see Table 14.2).
- Look for evidence of dual AVN physiology and the presence of an AP.
- If tachycardia is induced, atrial activation is observed to see whether it is via the AVN (AVNRT) or an AP (AVRT).
- Look for AVN block and bundle branch block at the onset/termination of tachycardia.
- His synchronous ventricular premature beats (HSVPBs) are introduced to identify whether an AP is mediating the tachycardia.

Atrioventricular block

- If AVN block occurs, but tachycardia persists, it is almost always an AT.

Onset

- AVN jump immediately followed by tachycardia: AVNRT.
- Loss of pre-excitation followed by tachycardia: AVRT.

Termination

- Last tachycardia complex atrial (block in AVN): AVNRT or AVRT (almost certainly not AT).
- Last tachycardia complex ventricular: AT (AVNRT or AVRT still possible).

His synchronous ventricular premature beats

- The aim is to introduce a ventricular paced beat exactly coincidental with the His potential during tachycardia, to see whether the ventricle is an essential component of the re-entry circuit (see Fig. 14.8).
- To do this, the cycle length of the tachycardia is measured, and a single sensed extra stimulus is delivered from the catheter in the RV at 20ms less than the cycle length.
- This is repeated, reducing the coupling interval by 10ms each time, until it is clear the sensed extra stimulus is pre-His.
- Tachycardia is then terminated, and the electrograms analysed.

Analysis

(See Fig. 14.8)

- HH and AA intervals are measured to ensure a stable tachycardia.
- The paced ventricular premature beat (VPB) must be synchronous with the His potential.

- The AA intervals before and after the HSVPB are measured. If the subsequent A is premature, this implies that the atrium *must* have been activated via an AP (as we know the His bundle is refractory due to the presence of the potential) and that the ventricle is part of the re-entry circuit, hence AVRT).
- If the A is not advanced, it suggests this is AVNRT.

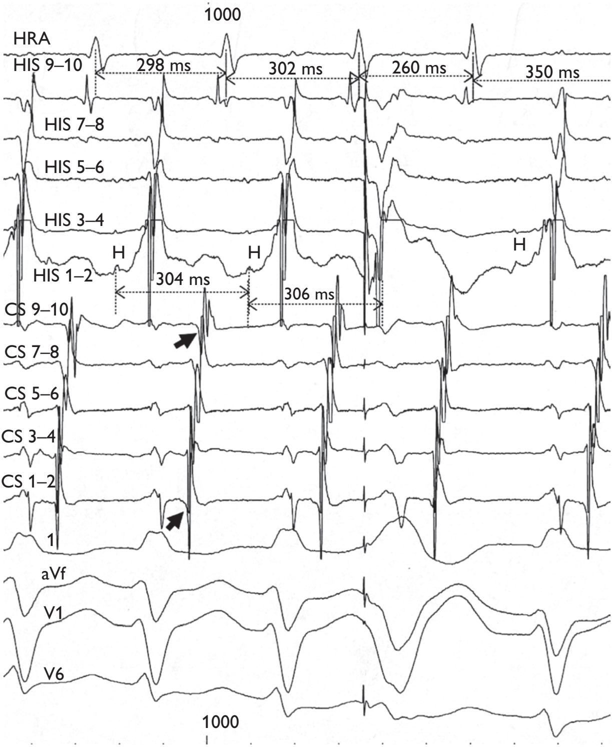

Fig. 14.8 His synchronous ventricular premature beats (HSVPB) resetting tachycardia. From top to bottom: intracardiac electrograms from high right atrium (HRA), His (HIS) bundle catheter (proximal to distal), coronary sinus (CS) catheter (proximal to distal), and four surface ECG leads. The tachycardia cycle length is ~300ms. During tachycardia, the earliest atrial activation is at the distal CS (lateral left atrium—see arrows), suggesting a left lateral accessory pathway. A sensed extra stimulus (the HSVPB) is introduced just ahead of the His potential (H). The next atrial complex is advanced (see cycle lengths measured at the HRA). This strongly suggests an AVRT mediated by a left lateral pathway.

Accessory pathways: overview

Definitions and ECG

- The atria and ventricles are separated by the fibrous annuli of the TV on the right and of the MV on the left.
- The AVN is the only electrical connection in normal hearts.
- Abnormal accessory pathways can occur at any position along these annuli and are named accordingly (see Fig. 14.9).
- They may conduct in one or both directions, and are the substrate for AVRT to occur.
- If an AP conducts anterogradely (from A to V), it will be manifest on the ECG as pre-excitation (short PR interval and delta wave). The morphology of the delta wave predicts the location of the AP.
- An AP that conducts only retrogradely is described as concealed.
- WPW syndrome strictly refers to APs that both manifest as pre-excitation on the resting ECG and cause tachycardia.
- The location of accessory pathways can be determined based on ECG characteristics (see Fig. 14.10).

Tachycardias

An AP can be associated with tachycardia via several mechanisms:

- *Orthodromic AVRT* (commonest, accounts for 95% of AP-mediated tachycardias)—narrow complex tachycardia
- *Antidromic AVRT*—broad complex tachycardia
- *Bystander*—SVT of another aetiology that conducts down the AP.

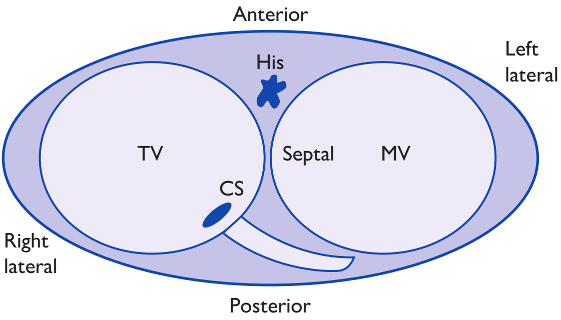

Fig. 14.9 Tricuspid (TV) and mitral valve (MV) annuli in cross-section. The coronary sinus (CS) is located at the posterior aspect of the heart. Accessory pathways can be positioned anywhere on the annuli (grey areas). They are named anatomically (i.e. anterior, left anterolateral, left lateral, left posterolateral, etc.). Anteroseptal pathways are close to the His bundle and atrioventricular node, and are termed parahisian.

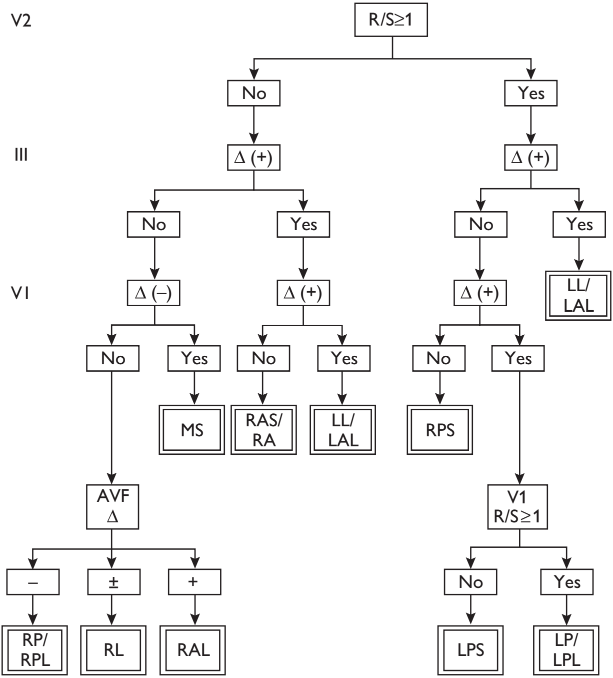
V2
III
V1
R/S≥1
No
Yes
Δ (+)
Δ (+)
No
Yes
No
Yes
Δ (–)
Δ (+)
Δ (+)
LL/ LAL
No
Yes
No
Yes
No
Yes
MS
RAS/ RA
LL/ LAL
RPS
AVF Δ
V1 R/S≥1
–
±
+
No
Yes
RP/ RPL
RL
RAL
LPS
LP/ LPL

Fig. 14.10 Algorithm to locate the accessory pathway from the ECG with pre-excitation. Δ = delta wave.

Reproduced from Chiang CE *et al*. *Am J Cardiol*, 1995; **76** (1): 40–6 with permission from Elsevier.

Prognosis

AF in the presence of an AP can be dangerous, as the ventricle is not protected by the decremental behaviour of the AVN. This can precipitate VF and sudden death. If patients are discovered incidentally, and are truly asymptomatic, then sudden death is extremely rare (between 1 in 2000 and 1 in 20,000 per annum). Invasive EP can be used to risk-stratify patients.

A worse prognosis is predicted by:

- Invasive EP testing:
    - Anterograde ERP of the AP <250ms (the longest interval that will not conduct down the AP during atrial extra stimulus pacing or AF)
    - Inducible AVRT
    - Multiple APs
- Symptomatic tachycardia
- Ebstein's anomaly.

Accessory pathways: management

Ablation

- APs can be cured by catheter ablation, and this is first-line treatment for symptomatic patients.
- A catheter is moved around the MV or TV annulus until the AP is located by finding the exact point of:
  - Earliest ventricular activation during SR or atrial pacing
  - Earliest atrial activation during ventricular pacing
  - Earliest atrial activation during orthodromic AVRT.
- Acute success is >90%. The complication rate is very low (death 0–0.2%, AVN block <1%). For parahisian AP, the risk of AVN block is higher and cryoablation is used if available.
- Left-sided pathways can be approached via the femoral artery, aorta, and LV, or from the RA by a trans-septal puncture.
- All symptomatic patients (with AVRT) should be offered ablation.
- Asymptomatic young patients (<35 years) or those in a high-risk profession (pilots, divers, etc.) should be considered for invasive EP testing and ablation. However, the risk of sudden death must be balanced against the complication rate of ablating the pathway (particularly if left-sided or parahisian).

Pharmacological

- Pharmacological management may be an appropriate alternative to ablation in some individuals (e.g. not symptomatic or non-recurrent).
- β-blockers or verapamil should be considered if there are no features of pre-excitation on the resting ECG.
- Flecainide and propafenone slow conduction in the AP without affecting the AVN and are the preferred agents if there are features of pre-exciting on a resting ECG.
- Drugs that slow AVN conduction only (e.g. digoxin) should not be used unless invasive EP has demonstrated that the AP does not conduct anterogradely (or conducts only very slowly).

Unusual pathways

Mahaim pathways

These are APs between the RA and RV (AV) or the RA and right bundle branch (atriofascicular). Unlike ordinary APs, they exhibit AVN properties of decremental conduction and sensitivity to adenosine. They only conduct anterogradely and mediate an AVRT with a broad complex LBBB appearance. They are successfully treated by catheter ablation.

Atrioventricular re-entry tachycardias: ablation

Atrioventricular re-entrant tachycardia

- Ablation must be performed during ventricular pacing or AVRT to identify the location of the AP (unless it is manifest on the resting ECG, i.e. WPW).
- The earliest atrial activation is sought. This is identified by using a mapping catheter in the atrium and is the location with an almost continuous V, then A electrogram.
- A true annular site is needed for success; this should manifest as an equal-sized atrial and ventricular component on the mapping catheter.
- Left-sided APs are approached either retrogradely (via the aortic valve and LV) or anterogradely (trans-septal puncture).
- VA conduction should be absent or via the AVN (concentric). If VA conduction persists, adenosine boluses are given to demonstrate both VA and AV block.

Atrioventricular node re-entrant tachycardia

- The target is the slow AVN pathway (see Fig.14.11).
- This is found inferior to the His bundle, close to the CS mouth.
- The presence of a slow pathway signal (bump and spike) with a small A and a large V component should be seen. Energy is delivered, and usually transient, slow junctional escape beats are seen as the cells die. If the catheter moves or any AV or VA block occurs, ablation is stopped immediately.
- If the lesion is therapeutic, a full EP study is then repeated to test and ensure no AVN damage.
- A successful procedural outcome is the inability to induce tachycardia, and complete loss of dual AVN physiology.
- Conventionally, the presence of a jump (see ➔ Dual atrioventricular nodal physiology, pp. 640–1) and a single echo beat (see Box 14.11) is permitted, providing tachycardia cannot be induced.
- If isoprenaline was needed to induce tachycardia, it must also be used during testing.

Box 14.11 Echo beats

- A premature atrial beat (or paced beat from the atrium) conducts through the atrioventricular node slow pathway into the atrium.
- This depolarizes the ventricles.
- The impulse then conducts back up the atrioventricular node via the fast pathway, depolarizing the atrium and creating a retrograde P wave.
- If the impulse were to go down the slow pathway again, this would be the start of an atrioventricular re-entrant tachycardia; if it does not, it is considered an 'echo' beat.

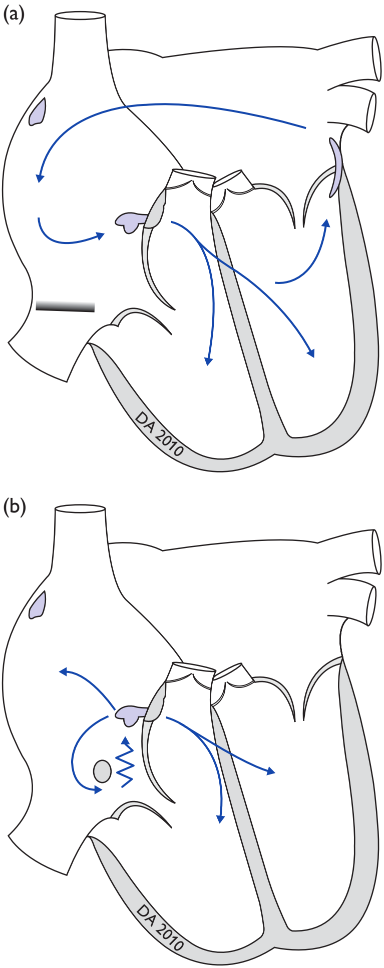

Fig. 14.11 Diagram exhibiting mechanisms of supraventricular tachycardia. Wavefronts are depicted by arrows. Orthodromic AVRT (a) via a left-sided accessory pathway (AP). Activation from A to V is down the atrioventricular node (AVN), then across the ventricular myocardium and back from V to A up the AP, thus completing the circuit. The ventricle therefore is an essential part of the circuit. Antidromic AVRT (not shown) would activate in the opposite direction. Typical AVNRT (b) activates from the atrium to the AVN via the slow pathway (zigzag arrow) and from the AVN to the atrium via the fast pathway, thus completing the circuit. The ventricle is activated as a bystander via the bundle of His and is not an essential part of the circuit.

Ventricular tachycardia: mechanism

Improved survival from MI and widespread use of ICDs have led to a much greater need for invasive management of VT (i.e. ablation). In structural heart disease, VT almost always has a re-entry mechanism. Normal heart VT may be focal or re-entry.

Structural heart disease

(See Fig. 14.12)

- Scarred ventricular myocardium (due to infarction, cardiomyopathy, etc.) provides the substrate for re-entry (see Fig. 14.1).
- Scar acts as a barrier to conduction (fixed block); however, damaged, but viable myocardium will provide areas of slow conduction, which are critical to allowing re-entry circuits to form.
- This acts as a source of wavefronts that repeatedly depolarize the rest of the ventricle—hence monomorphic VT.
- LV scarring is much more common than RV scarring, other than in ARVC.
- A stable re-entry circuit can break down into chaotic activation (i.e. VF), hence the link between VT and sudden death.
- *Bundle branch VT:* occurs in severely impaired ventricles, with damage to the conducting system and usually pre-existing bundle branch block. It is due to a re-entry circuit involving the right and left bundles.

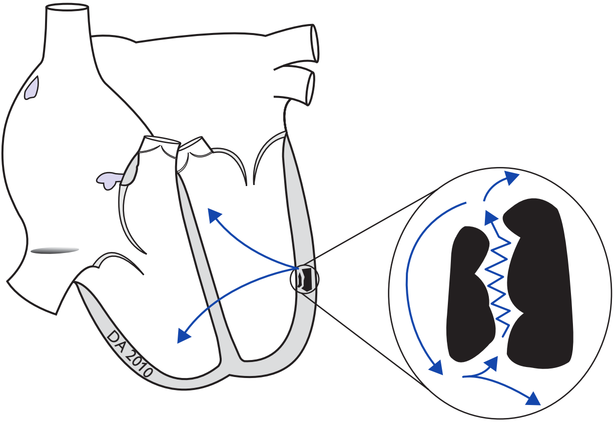

Fig. 14.12 Mechanism of ventricular tachycardia (VT) in structural heart disease (e.g. post-myocardial infarction). An area of scar in the left ventricularl myocardium (black) provides fixed conduction block. Electrical wavefronts (arrows) rotate around and slowly through the scar to form a re-entry circuit. This acts as a source of wavefronts to the rest of the ventricle. The area of slow conduction (zigzag arrows) is termed the diastolic pathway, as it activates during ventricular diastole. During VT, intracardiac electrograms recorded here are timed with the midpoint between successive QRS complexes. This is the target for ablation of VT.

Normal heart ventricular tachycardia

- *RVOT (and LVOT) VT:* has a focal mechanism with cells exhibiting enhanced automaticity; can, less commonly, occur from elsewhere in the RV or LV.
- *Fascicular VT:* is probably a re-entry circuit within either the posterior (usually) or the anterior (rare) hemifascicles of the left bundle.

Ventricular tachycardia: ablation

Clinical indications

- Incessant VT or electrical storm secondary to scar-related heart disease (ESC Class I recommendation).
- Recurrent ICD shocks due to sustained VT in those with IHD (ESC Class I recommendation).
- After a first episode of sustained VT in those with IHD and an ICD (ESC Class IIa recommendation).
- Recurrent VT/VF/electrical storm in those with ACS despite complete revascularization and OMT (ESC Class IIa recommendation).
- Ablation is recommended in those with normal heart VT if symptomatic, where AAD therapy has failed, or there is a decline in LV function (ESC Class I recommendation).

Activation mapping ventricular tachycardia

- To successfully map the re-entry circuit, the patient must be in VT and therefore, it needs to be haemodynamically well tolerated.
- Remote defibrillation paddles are attached to the patient, so that if VF or hypotensive VT occurs, it can be immediately cardioverted.
- If feasible, the LV is accessed retrogradely (via the femoral artery) and anterogradely (via the femoral vein and a trans-septal puncture).
- Using a 3D mapping system, the ablation catheter is moved around the LV recording ICegrams and timing them to a fixed reference.
- The aim is to identify the critical diastolic pathway at which the circuit is most susceptible to destruction.

Entrainment of ventricular tachycardia

- This can only be done on tachycardias with a re-entry mechanism.
- The ablation catheter is moved around the ventricle to sites where the circuit is expected (i.e. adjacent to areas of scar).
- The ventricle is paced at a rate just faster than the tachycardia; a VT is entrained if it follows the same circuit, but at a faster rate.
- If the ECG during pacing is a 12/12-lead match to the clinical VT, then this is concealed entrainment. This implies the catheter is within the critical diastolic portion of the circuit. To confirm this, when pacing is stopped, the return cycle length (time from the final paced beat to the next activation at the catheter) should be almost identical to the tachycardia cycle length.

Ablation technique

The standard steps of a VT ablation are:

- *Inducing VT* (see ➔ Programmed ventricular stimulation, p. 644): ensure well tolerated and similar to clinical VT
- *Mapping VT to identify the critical diastolic pathway:*
    - Very early local ICegram occurring mid diastole (50–150ms ahead of ECG)
    - Concealed entrainment during pacing
    - Return cycle length (= post-pacing interval) < tachycardia cycle length + 30ms

- *Deliver RF energy*: via an irrigated catheter (for deeper lesions) at the site meeting the criteria above.
- If VT is terminated, attempt to reinduce.

Substrate ablation of ventricular tachycardia

- If VT is not haemodynamically tolerated or cannot be induced, then activation and entrainment mapping cannot be performed.
- An alternative is to use a 3D mapping system to create a map of the LV during SR. The map displays the voltages of the ICegrams, and hence areas of scar are identified.
- The re-entry circuit of the clinical VT can be estimated from the 12-lead ECG and by pacing at sites on the edge of scar, which, if they are the location of the re-entry circuit driving VT, will give a similar 12-lead ECG appearance to that of the clinical VT.
- Ablation is delivered between two areas of fixed conduction block (scar, mitral annulus) to interrupt theoretical re-entry circuits.

Failed ablation

If conventional ablation fails, alternative approaches are:

- Ablating the epicardial surface of the heart by delivering the catheter via the pericardium (as for a pericardial aspiration)
- Alcohol ablation via a small terminal coronary branch subtending the scarred area supporting re-entry—hence, give the patient a controlled small MI that destroys the critical portion of the re-entry circuit
- Cardiac surgical ablation.

Permanent pacemakers: overview

Introduction

- PPMs play a central role in the management of bradycardia.
- They can be used to treat atrial and ventricular tachyarrhythmias (with ICDs).
- They can improve ventricular function and symptoms in CCF (CRT).
- Basic pacemaker function involves sensing and pacing either the atria or the ventricles, or both.
- Indications for pacing are outlined in Box 14.12.

Box 14.12 Indications for permanent pacing

Class I

- Sinus node disease with symptoms due to bradycardia or pauses
- Third-degree or second-degree (Mobitz type 2) atrioventricular (AV) block
- Bundle branch block with unexplained syncope and abnormal electrophysiology study
- Alternating bundle branch block
- Recurrent unpredictable syncope in patients with dominant cardioinhibitory carotid sinus syndrome
- Patients aged >40 years with recurrent unpredictable reflex syncope and documented symptomatic pauses (>3s) or asymptomatic pauses (>6s) due to sinus arrest or AV block
- Symptomatic patients with tachycardia-bradycardia sinus node disease to correct bradycardia and allow treatment of tachycardia

Class IIa

- Second-degree (Mobitz type 1) AV block which causes symptoms
- First-degree AV block (>300ms) with persistent symptoms similar to pacemaker syndrome

Glikson M, *et al*. 2021 ESC guidelines on cardiac pacing and cardiac resynchroniza-tion therapy. *Eur Heart J*. 2021;**42**:3427–520.

International code

This is a 5-letter identification code describing the function of the pacing system (see Table 14.3). Most pacemakers can be described using the first three letters only.

Table 14.3 NASPE/BPEG generic code for permanent pacemakers

Letter	Meaning	Options
First letter	Chambers paced	O—none A—atrium V—ventricles D—dual (A + V)
Second letter	Chamber(s) sensed	O—none A—atrium V—ventricles D—dual (A + V)
Third letter	Response to sensing	O—none T—triggered I—inhibited
Fourth letter	Rate modulation	O—none T—triggered. Sensed activity results in triggering of pacing I—inhibited. Sensed activity results in inhibition of pacing.
Fifth letter	Multisite pacing	O—none A—atrium V—ventricles D—dual (A + V)

NASPE, North American Society of Pacing and Electrophysiology; BPEG, British Pacing and Electrophysiology Group.

Bernstein AD, *et al*. The revised NASPE/BPEG generic code for antibradycardia, adap-tive-rate, and multisite pacing. North American Society of Pacing and Electrophysiolo-gy/British Pacing and Electrophysiology Group. *Pacing Clin Electrophysiol*.2002;**25**(2):260–4.

PPM: implantation

- *Antibiotic prophylaxis:* reduces the risk of infection. Should be given before the procedure begins. Use a drug that is effective against staphylococci (e.g. flucloxacillin; vancomycin if penicillin-allergic).
- *Site of implant:* usually infraclavicular (left-sided if right-handed); rarely abdominal, axillary, or sub-mammary.
- *Incision:* an incision should be made beneath the clavicle (or, less commonly, in the deltopectoral groove), and a dissection made down to the pectoral muscle.
- *Pocket:* should be created by blunt dissection (often with fingers). Usually subcutaneous, occasionally submuscular (beneath the pectoralis major).
- *Venous access:* a direct cut-down to the cephalic vein in the deltopectoral groove or Seldinger approach to the subclavian/axillary vein. A venogram (from the ipsilateral brachial vein) is useful if access is difficult. Rarely, the internal jugular or femoral veins are used.
- *Leads:* active (screw-in) or passively fixed. Active fixation leads are generally used in the atrium.
- *Lead placement:* leads should be advanced into the appropriate cardiac cambers (usually RA and RV). Fluoroscopy should be used for direct visualization as necessary. Leads should be advanced to the RV apex for the ventricular lead, and the RA appendage for the atrium (see Fig. 14.13 for lead placement, and Table 14.4 for acceptable parameters). His bundle pacing is occasionally used (see Box 14.13).

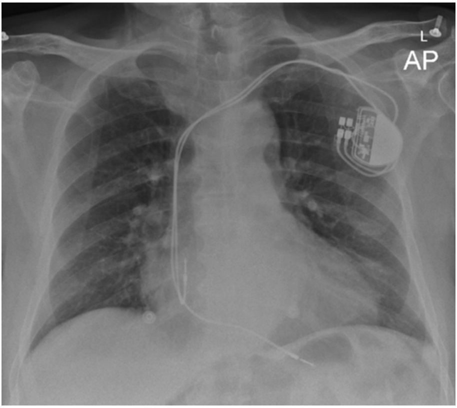

Fig. 14.13 Anteroposterior chest X-ray post-permanent pacemaker implantation, showing satisfactory placement of actively fixed leads into the right atrial appendage and right ventricular apex. The generator has been placed subcutaneously in the standard left infraclavicular position.

Table 14.4 Acceptable pacing parameters for new leads

	Atrium	Ventricle
Threshold[a]	<1.5V	<1.0V
Sensitivity (P/R wave)	>1.5mV	>4.0mV
Slew rate	>0.2V/s	>0.5V/s
Impedance[b]	400–1000 ohms	400–1000 ohms

[a] Using a pulse width of 0.5ms.

[b] Some 'high impedance' leads are designed to have an impedance of >1000 ohms.

Box 14.13 His bundle pacing

- Placing the right ventricular (RV) lead in a non-apical position has been considered.
- Locating the RV lead to activate the His bundle may improve coordination of LV depolarization and contraction.
- This placement has been associated with ↑ LVEF in those with LVEF <45% prior to implant compared with apical positioning.
- In those with an indication for a cardiac resynchronization therapy (CRT) device, His pacing may be a possible alternative.
- No difference has been seen in those with normal LVEF prior to implantation, and complication rates are similar to those with apical pacing.
- The HOPE-HF trial is currently under way to assess the effects on exercise capacity in those with heart failure but who are not eligible for a CRT device. The His-SYNC will examine His pacing for improvement in LVEF in those with a conventional CRT indication.

- *Suturing:* once positioned, lead sleeves should be firmly stitched to muscle with a non-resorbable suture (silk, Surgilon™, etc.). The pocket is closed in layers. Skin closure is with sutures or Dermabond glue. Suture material for pocket/skin closure is operator-dependent.
- *Follow-up:* ensure stitches are removed (if non-absorbable) and the wound is healed. Pacing check within 4–6 weeks (see later).

PPM: which pacing modality?

The vast majority of patients should have atrial-based pacing (i.e. either AAI or DDD). Ventricular-only pacing leads to a greater incidence of AF and potential pacemaker syndrome (see Fig. 14.14).

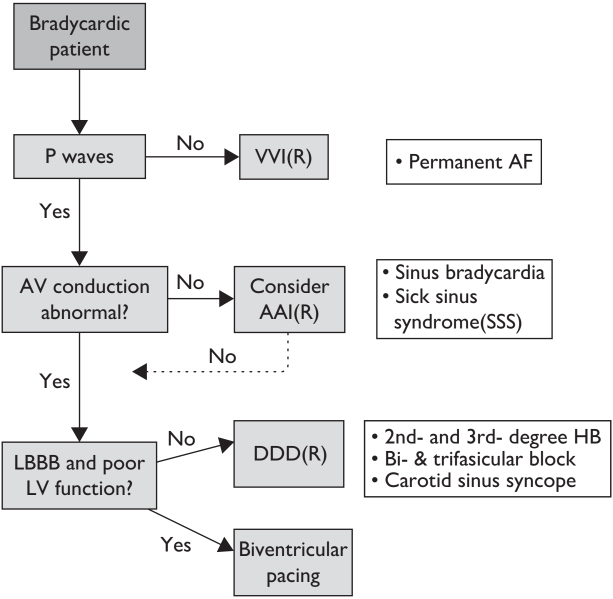
Bradycardic patient
P waves
No
VVI(R)
• Permanent AF
Yes
AV conduction abnormal?
No
Consider AAI(R)
• Sinus bradycardia
• Sick sinus syndrome(SSS)
No
Yes
LBBB and poor LV function?
No
DDD(R)
• 2nd- and 3rd- degree HB
• Bi- & trifasicular block
• Carotid sinus syncope
Yes
Biventricular pacing

Fig. 14.14 Which pacing modality? Caution should be used when considering an AAI pacemaker and should be considered principally in those where there is a reason to avoid having two leads (e.g. young age or limited venous access).

PPM: complications of pacing

At the time of implantation

The procedural complication rate is 5%. Important complications are:

- *Haematoma:* most can be managed conservatively, but evacuation is required if very large or threatening the skin (usually due to an arterial bleed). Meticulous haemostasis should be secured during the implant, and diathermy used if necessary. Bruising over the site is common and resolves spontaneously.
- *Pneumothorax:* a small apical pneumothorax may be observed with serial X-rays if the subclavicular or axillary veins have been used. A chest drain is required for anything larger. A haemothorax may coexist.
- *Pericardial effusion:* more common with actively fixed leads, which can perforate through the thin-walled RA or RV. Pericardial tamponade can occur, requiring urgent pericardiocentesis.
- *Infection:* occurs at the time of implant but usually presents late. Minimized by aseptic technique and antibiotic prophylaxis.
- *Air PE:* care must be taken when using sheaths, as a significant volume of air can be drawn into the vein.
- *Axillary vein thrombosis:* rare, can present with a swollen arm and is treated with systemic anticoagulation.

Late complications

- *Lead displacement:* this is common and requires lead repositioning.
- *Infection:* risk factors are fever within 24h of implant, use of a temporary wire, prolonged procedure, and any revision procedure shortly after the first implant. Infection can manifest as localized pocket abscess/cellulitis, septicaemia, or endocarditis with vegetations on the leads. Treatment is urgent extraction of the entire system. Prolonged IV antibiotic therapy may be needed. Patients who are pacing-dependent will need a temporary wire. New device implantation should be performed when there are no signs of infection, on the contralateral site.
- *Box or lead erosion:* at implant, care must be taken to create a large enough pocket for the device and leads without causing tension on the skin. Indolent infection can cause erosion. If the skin is threatened, box repositioning may be attempted (to a submuscular pocket), but if the skin is breached, the whole system needs to be explanted.
- *Lead damage/failure:* common causes are crush between the clavicle and the first rib, or in the pocket if the leads have been coiled too tightly. Fibrosis at the lead tip results in higher pacing thresholds and poor sensing. Lead failure requires insertion of a new lead (see Fig. 14.15).
- *Device failure:* rare.
- *Venous obstruction:* this is usually asymptomatic (due to collateral formation) but may present a problem at system revision.

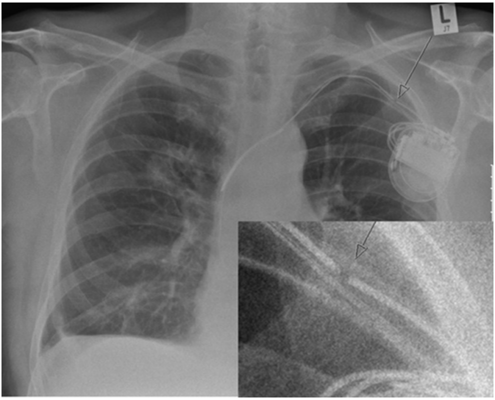

Fig. 14.15 Atrial lead fracture. A dual-chamber implantable cardioverter–defibrillator was implanted 3 years prior to this posteroanterior chest X-ray. At routine follow-up, the pacing impedance was very high and there was no atrial sensing or capture. The atrial lead has fractured (arrow). The inset shows a magnified view of the fracture (arrow).

Other problems

- *Pacemaker syndrome:* this occurs in patients who have sinus node function but are implanted with a VVI pacemaker. Symptoms include: presyncope, syncope, light-headedness, fatigue, exercise intolerance, malaise, lethargy, and dyspnoea. It is due to independent atrial and ventricular contraction. Treatment is to restore AV synchrony, by either reducing the pacing rate or inserting an atrial lead.
- *Pacemaker (endless loop) tachycardia:* this occurs in dual-chamber pacing (VDD, DDD, or DDDR) and is caused by inappropriate sensing of retrograde P waves, and hence triggering a ventricular response. Treatment is to ↑ the post-ventricular atrial refractory period (PVARP), so as not to sense the retrograde P wave.
- *ATs:* can cause rapid ventricular pacing in dual-chamber systems by sensing the atrial rate. To overcome this, the pacemaker can either mode-switch to VVI or be reprogrammed to the DDI mode.

PPM: follow-up

Magnet response

- When the pacemaker is within a sufficiently strong magnetic field, it reverts to its magnet mode.
- This is non-sensing fixed pacing at the device's 'magnet rate' of usually 90–100/min (i.e. DOO (dual chamber) or VOO/AOO (single chamber)).
- Application of a magnet over the pacemaker can be used during surgery to prevent device inhibition (and hence asystole) when diathermy is being used.

Pacemaker clinic

- The device is interrogated every 6–12 months.
- At these visits, the function of the lead(s) is assessed by checking the pacing threshold, sensitivity (the size of sensed electrogram detected), and pacing impedance.
- Any change in these parameters could indicate a problem; for example, a low impedance suggests an internal insulation break, whereas a high impedance might suggest a lead fracture.
- The battery voltage is measured, and below a critical level, the elective replacement indicator (ERI) activates. There is ~6 months between ERI and the potentially dangerous EOL (end of life).
- A box change is usually arranged within a few months after the ERI is activated.

Interference

- *MRI:* previously absolutely contraindicated in a patient with a pacemaker or an ICD, as it can cause device malfunction and harm the patient. However, 'MRI-safe' pacemaker and ICD/CRT systems are available and are generally considered as first-line devices for implantation.
- *Radiotherapy:* can damage pacemaker electronics or result in erosion of the generator. Damage is cumulative and the device should be shielded. Occasionally, the generator may need to be repositioned if it overlies a tumour (e.g. lung cancer).
- *Diathermy:* may inhibit pacing. The device should be reprogrammed to a non-sensing mode (VOO) prior to surgery or have a magnet applied during surgery. The pacemaker needs to be checked after surgery to ensure normal function.
- *Security gates:* these will be activated by pacemakers. Patients are advised to carry their identification card, so they can show staff.

Implantable cardioverter–defibrillators: overview

- Mirowski implanted the first automatic ICD in 1980. Since then, there has been dramatic improvement in technology, and evidence to support their use.
- Initial ICDs were large and placed surgically in the abdomen.
- ICDs are now implanted in the same way as pacemakers and are often part of a biventricular pacing system.

Components

- The bulk of an ICD box is the battery and capacitors that generate and store the energy to deliver a defibrillation shock.
- The box is attached to a ventricular 'shock' lead and often an atrial 'pace-sense' lead.
- The V lead contains one or two shocking coils and bipolar pacing electrodes at its tip. This senses electrograms and can deliver low-voltage pulses to pace the heart if it is too slow (bradycardia pacing), or overdrive if it is too fast (e.g. in VT (anti-tachycardia pacing)).
- Microprocessors contain the algorithms that interpret electrograms to: (1) detect tachycardias; (2) discriminate VT/VF from non-life-threatening arrhythmia (e.g. AF); and (3) deliver therapy. These algorithms contain features that are both programmable and fixed.

Preimplantation

- Many patients find receiving shocks or the fear of receiving shocks distressing. All patients should be counselled prior to implantation.
- Quality of life issues should be discussed prior to implantation.
- End-of-life care should be discussed prior to implantation.
- In those with recurrent inappropriate shocks after implantation, further assessment of psychological status should be undertaken.

Implantation

- Transvenous ICDs are implanted in a way identical to that for pacemakers, and the same complications occur (see ➔ PPM: complications of pacing, pp. 680–1).
- A range of leads are available: active/passive, single coil/dual coil.
- Extra vigilance is needed over selecting a V lead position with good electrogram sensing (ideally R wave >10mV).

Defibrillation threshold testing

- Defibrillation threshold testing (DFT) may be performed once the ICD is implanted, as ventricular electrograms in VF will be of much lower amplitude than during SR.
- The patient is sedated and VF is induced. The ICD is then observed to ensure it successfully detects and terminates VF. If the device fails, an external shock is delivered and the lead is repositioned.
- During testing, the ICD is programmed to its *least* sensitive detection and delivers an energy that is ≥*10J below* its maximum output.
- After the procedure, the ICD is programmed to its most sensitive detection and delivers shocks at *maximum* energy. In this way, there is a safety margin that reduces the chance of the device failing.

Indications for implantable cardioverter–defibrillators

Class I

- *Survivors of cardiac arrest secondary to VT or VF:* in the absence of reversible factors and patient receiving optimal medical therapy
- *Haemodynamically poorly tolerated sustained VT:* with significant structural heart disease (including ARVC, HCM, DCM, etc.)
- *Ischaemic heart disease:* >40 days after MI, LVEF ≤35%, and NYHA classes II–III
- *Non-ischaemic heart disease:* LVEF ≤35% and NYHA classes II–III
- *Congenital heart disease:* LVEF <35%, NYHA classes II–III, and biventricular pathology despite optimal medical therapy
- *Short QT syndrome/Brugada syndrome:* with spontaneous sustained VT
- *CPVT:* with recurrent syncope or previous sustained VT
- *Myotonic dystrophy:* with non-bundle branch block VT.
- *Myocarditis:* sustained VT in chronic phase of myocarditis

Class IIa

- *Recurrent sustained VT:* normal LV and optimal medical therapy
- *LVEF ≤35%:* with ≥3 months of optimal medical therapy
- *HCM:* if 5-year risk of SCD ≥6%, or if risk 4–6% with significant LGE on CMR, LVEF <50%, or other risk factors
- *ARVC:* sustained VT, arrhythmic syncope, or RV/LV dysfunction
- *DCM:* confirmed *LMNA* mutation and 5-year risk of ventricular arrhythmia ≥10%, and NSVT during ambulatory monitoring or LVEF <50%
- *Brugada syndrome:* with spontaneous type I ECG pattern and syncope
- *Cardiac amyloidosis:* with VF or haemodynamically unstable VT
- *Congenital heart disease:* with syncope of unknown origin and sustained VT/VF on programmed ventricular stimulation
- *Tetralogy of Fallot:* with multiple SCD risk factors
- *Myotonic dystrophy:* without AV conduction delay and syncope highly suspicious for ventricular arrhythmia, or high suspicion of ventricular arrhythmia and non-bundle branch block VT induced
- *Myocarditis:* haemodynamically not-tolerated sustained VT/VT during acute phase
- *Sarcoidosis:* if indicated for permanent pacing or if significant LGE on CMR after resolution of acute inflammation

Class III (ICD definitely not indicated)

- *Life expectancy:* patients who are not expected to survive ≥1 year
- Significant psychiatriac comorbidity that may be worsened by implant or cause problems with follow-up
- *Ischaemic heart disease:* primarily prevention <40 days after MI
- *VT/VF with a reversible cause:* for example, severe sepsis with normal heart, or normal heart VT amenable to curative ablation

Adapted from Zeppenfeld K, *et al*. 2022 ESC guidelines for the management of pateitns with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022:**43**: 3997–4126.

Subcutaneous ICDs

- Subcutaneous ICDs (S-ICDs) were developed due to recurrent problems with transvenous leads and cardiac access through the vascular system.
- The system consists of a specific ICD box which sits on the lateral chest wall, and a defibrillator lead with a proximal and a distal electrode.
- Inherently, an S-ICD cannot provide pacing support if bradycardia develops and is unable to deploy anti-tachycardia pacing therapy.

Indications

- S-ICDs should be considered as an alternative to transvenous systems in patients with an indication for an ICD where pacing therapy for bradycardia support, CRT, or anti-tachycardia pacing are not required (ESC Class IIa recommendation).

Preimplantation

- Preimplantation screening is required to ensure that an appropriate shock vector is available and to reduce the chances of inappropriate shocks being delivered after implantation.
- Patients have electrodes placed in the same locations in which they would be implanted and ECG patterns obtained.
- Often patients are exercised (where able) to ensure that the signal does not change substantially.

Implantation

- The device is implanted either under general anaesthesia or by using a local anaesthetic and sedation.
- An incision is made on the lateral chest wall, with the pocket between the serratus anterior and the latissimus dorsi.
- A second incision is made towards the bottom of the sternum (two-incision technique), with an additional incision occasionally made on the superior sternum (three-incision technique).
- The lead is tunnelled from the incision on the lateral chest wall to the inferior sternal incision, and then advanced superiorly up the sternal wall (see Fig. 14.16).
- After implantation, a DFT is normally undertaken.

Post-procedure

- Patients should have both a posterior–anterior and lateral chest radiograph to confirm the position.
- *Posterior–anterior CXR:* the pulse generator should be in line with the cardiac apex, whereas the subcutaneous lead should be on the left of the mid-sternal line.
- *Lateral CXR:* the pulse generator should be present and should generally bisect the mid-axillary line, and the subcutaneous lead should lie just superior to the sternum.

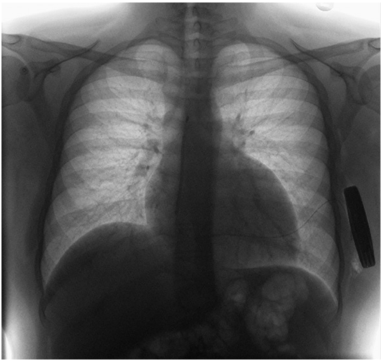

Fig. 14.16 Posterior–anterior chest radiograph showing an appropriately positioned subcutaneous implantable cardioverter–defibrillator.

Copyright © Fielder Camm.

ICD: programming

Detection of tachycardias

- The ICD measures the intervals (cycle length) between successive sensed ventricular electrograms, and hence measures the ventricular rate.
- If the rate enters a programmed zone (e.g. >190bpm), then tachycardia is detected.
- Most devices allow multiple detection zones (e.g. VT 170–200; fast VT 200–230; and VF >230).
- Each zone can be programmed with different therapies.
- If no therapies are programmed, it is a monitor zone.

Discrimination of SVT from VT/VF

- Not all tachycardias at a rate >170 bpm are VT.
- SVTs (e.g. sinus tachycardia, AVNRT, AVRT, AF) can all reach a V rate of >170bpm.
- Discrimination algorithms attempt to distinguish these arrhythmias and prevent inappropriate and painful therapy (see Box 14.14).
- Very fast V rates (e.g. >220bpm) are almost always VT/VF, and discrimination generally is not applied.

Box 14.14 Discrimination of SVT from VT/VF

Discrimination algorithms in ICDs use a combination of the following parameters:

- AV association:
  - V > A: always VT/VF
  - V = A: SVT or VT
  - V < A: likely AF or atrial tachycardia; VT possible (e.g. AF and VT)
- Electrogram morphology in tachycardia:
  - Same as SR: SVT
  - Different from SR: VT or SVT + bundle branch block
- Onset of tachycardia:
  - Sudden: SVT or VT
  - Gradual: sinus tachycardia
- Stability of VV intervals during tachycardia:
  - Not stable: AF or VF
  - Stable: SVT or VT

Therapies

Once the device detects tachycardia and decides it is definitely VT or VF, it will use one of two forms of treatment, depending on how the zone has been programmed. Therapies are disabled in a magnetic field.

Anti-tachycardia pacing

- This is a burst/train of pacing that attempts to overdrive and terminate VT, but is not effective for VF.
- The device delivers a set number of pulses (6–12) at a fixed cycle length that is a percentage of the measured tachycardia cycle length (often 81%).
- The sequences may be repeated with shorter cycle lengths (i.e. pace faster).
- Within the train of pacing, the cycle length can be shortened (= ramp pacing); no advantage of ramp over burst in clinical trials.
- If anti-tachycardia pacing fails to terminate VT, a shock is usually delivered.

Defibrillation

- ICDs deliver a maximum energy of up to 42J as a biphasic waveform from the shocking coil on the RV lead to the pulse generator.
- The shocking vector travels superiorly from the RV, including most of the IV septum and LV.
- If a dual-coil lead or separate SVC coil is implanted, the device can shock either between both coils or between the ICD box and either coil.
- All programmed shocks should be at the device's maximum output.

ICD: troubleshooting

Follow-up

- The patient's ICD is interrogated every 6–12 months either in clinic or remotely via wireless receivers installed in the patient's home.
- Checks are made on the lead parameters and battery life (to determine whether a box change is necessary).
- The arrhythmia log is reviewed to determine if there have been any ventricular or atrial arrhythmias and any therapy delivery.
- Remote follow-up allows automatic downloads of important events (red alerts) (e.g. episodes of VF, impending battery failure, damage to the lead, etc.). These are communicated directly to the ICD clinic.

VT/VF storm

- This is defined as ≥3 appropriate shocks for VT/VF in <24h.
- Common causes are ischaemia, worsening HF, electrolye imbalance, change in medication, or intercurrent illness. Sometimes no obvious cause is found.
- Patients should be managed in specialist EP centres for optimization of AADs and device programming ± VT ablation.

Inappropriate shocks

- The most important ICD-associated morbidity; occur in 10–20% of patients.
- A shock delivered in an unsuspecting patient is painful and frightening. Can lead to psychiatric problems (e.g. anxiety, depression).
- They are due to poor programming, VT without haemodynamic compromise, AF with fast ventricular rates, other SVT, lead damage, or external interference (e.g. diathermy).
- In an emergency, a magnet placed over the device will disable therapies, so the cause can be determined.

Drug interactions

- AADs may ↑ defibrillation thresholds (e.g. flecainide, propafenone, amiodarone).
- They may also slow the rate of VT, such that it no longer falls in the programmed detection zone (e.g. β-blockers).
- Ensure ICDs are still effective after major drug changes.

End-of-life issues

- Patients with advanced heart disease may reach a palliative phase (NYHA class IV) or develop another terminal illness (e.g. cancer).
- After careful counselling with the patient, family, and palliative care team, it may be appropriate to turn therapies off or not to replace a box that has reached the end of its battery life. These are difficult decisions; a multidisciplinary approach is necessary.
- Devices need to be turned off when patients have died, and explanted before cremation.
- In acute end-of-life scenarios in patients with ICDs, a magnet can be placed over the box, which will turn off all therapies.

Cardiac resynchronization therapy

- Patients with CCF and broad QRS (particularly LBBB) on their ECG will have uncoordinated contraction and relaxation of the ventricles because of delayed and heterogeneous depolarization of the LV (dyssynchrony).
- When pacing the RV and LV simultaneously, CRT improves coordinated ventricular contraction, ↑ CO, and reduces CCF symptoms (see Box 14.15).

Box 14.15 Current indications for cardiac resynchronization therapy

Class I

- CCF established on optimal medical therapy, in sinus rhythm with LBBB, sinus rhythm QRS duration ≥150 ms, and LVEF ≤35%
- If LVEF <40%, CRT is recommended of PPM when indication for ventricular pacing
- In those with AF and HFrEF undergoing AV node ablation

Class IIa

- CCF established on optimal medical therapy, sinus rhythm LBBB ECG, with QRS duration 130–149ms and LVEF ≤35%
- CCF established on optimal medical therapy, sinus rhythm non-LBBB ECG, with QRS duration >150ms and LVEF ≤35%
- In AF with CCF, with LVEF ≤35% despite optimal medical therapy and QRS duration ≥130ms
- Upgrade from PPM/ICD to CRT in patients developing CCF, with LVEF ≤35% on optimal medical therapy and significant proportion of RV pacing

Glikson M, *et al*. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;**42**:3427–520.

Electrical or mechanical dyssynchrony?

- Mechanical dyssynchrony detailed by echocardiography, including tissue Doppler, does not predict who respond to CRT, and therefore electrical dyssynchrony (i.e. broad QRS on ECG) remains the standard measurement.
- CRT is not recommended in patients with narrow QRS complexes, even with evidence of mechanical dyssynchrony.

Implantation

- The RA and RV leads (often an ICD lead) are inserted conventionally.
- The LV is paced epicardially via the CS.
- Using a Seldinger technique, a guide catheter is introduced into the RA via the subclavian vein (SCV).
- The CS is intubated, and venography performed to identify a suitable lateral tributary.

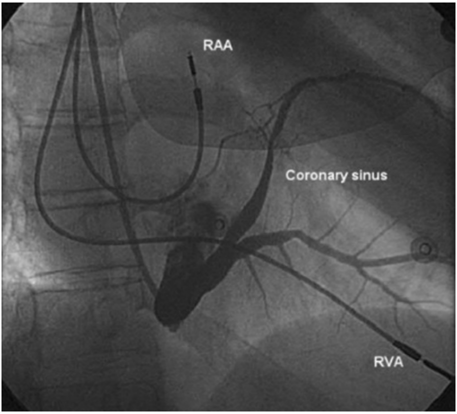

Fig. 14.17 A fluoroscopic image of the heart from the right anterior oblique projection. There is an active fixation lead in the conventional right atrial appendage and a lead in the right ventricular apex. Dye has been injected from below retrogradely up the coronary sinus to demonstrate the lateral left ventricular branches, from where pacing stimuli can capture the ventricle.

- The pacing lead is then inserted, either with a stylet or by using the over-the-wire technique, into a stable position, with acceptable pacing parameters and no diaphragmatic stimulation (see Fig. 14.17).
- There are a number of tools to help place the lead (e.g. subselector sheaths) and different leads (e.g. steerable or 'active' fixation).
- If the anatomy is unfavourable (tortuous, small veins) or there is inability to capture the LV, patients can be referred to a cardiac surgeon for thoracoscopic-guided epicardial lead placement.
- A wireless LV pacing system (WiSE-CRT) is also available and is implanted endocardially.

Effects of cardiac resynchronization therapy

- Some patients respond immediately, whereas the majority respond over a course of weeks.
- The benefit can be dramatic, with a major improvement in quality of life, reduced hospitalizations, and improved prognosis.
- There are improvements in LVEF and a reduction in ventricular dimensions (reverse remodelling).
- Implantation of devices in asymptomatic patients can delay symptom onset and reduce future hospitalization episodes for CCF.

Non-responders

Unfortunately, 30–40% of patients who undergo CRT implantation fail to respond. Reasons for this are: suboptimal lead position, end-stage CCF (NYHA class IV), and alternative causes of symptoms (e.g. COPD). There are a number of options for these patients:

- *Pacing percentage:* BiV pacing should be as close to 100% as possible. Parameters should be altered to achieve this.
- *Echo-guided optimization:* CO is assessed for different AV and RV–LV pacing intervals, with the optimal settings chosen.
- *Lead repositioning:* the LV lead can be moved to a different site (targeted to the latest activated LV segment).
- *Multisite pacing:* implanting an additional LV lead via another CS branch. If this is not possible, then two RV leads can be implanted (apex and high septum).

Implantable loop recorders

- ILRs are small devices that are placed subcutaneously and allow long-term monitoring of cardiac rhythm.
- ILRs tend to have a battery life of ~3 years.

Indications

- Patients with recurrent syncope of uncertain origin, without high-risk features, and a high likelihood of recurrence within the battery life of the device (ESC Class I recommendation).
- Patients with syncope with high-risk features in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment and who do not meet criteria for an ICD or PPM (ESC Class I recommendation).

Implantation

- Performed using local anaesthetic.
- A small incision is made on the anterior chest wall and the device is inserted.
- Exact implantation techniques vary slightly across devices.

Follow-up

- Most ILRs automatically download any concerning traces for review by the linked hospital pacing team.
- ILRs can be removed after a diagnosis is made or when the battery is depleted.

Chapter 15

Practical procedures

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Arterial line insertion *700*
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Arterial blood sampling

An arterial blood sample is used to measure the arterial oxygen tension (PaO_2), carbon dioxide tension ($PaCO_2$), pH and bicarbonate/base excess levels, and Hb saturation (SaO_2).

Indications

- To obtain information on acid–base balance.
- To obtain fast information on Na^+ or K^+ levels (will need to confirm findings with laboratory findings). Occasionally creatinine levels can be obtained.
- To obtain lactate levels.
- To obtain information about oxygenation status of the patient.

Contraindications

- Poor collateral circulation/significant peripheral vascular disease in the limb.
- Cellulitis surrounding the site.
- AV fistula.
- Coagulopathy/thrombocytopenia (relative contraindication).

Equipment required

- 1% lidocaine.
- 2mL syringe.
- 25G (orange) needle.
- ABG kit—23G (blue) needle, 2mL heparinized syringe, plastic bung.
- Gauze.
- Gloves.
- 70% isopropyl alcohol wipe.

General procedure

- Wash hands; identify the patient, and put gloves on.
- Undertake Allen's test (see Box 15.1).
- Clean the site with an alcohol wipe.
- Infiltrate the subcutaneous space (not into the vessel) with lidocaine.
- Locate the artery through palpation.
- Insert the 23G needle attached to a heparinized syringe through the skin at a 40° angle distal to the point of palpation.

Box 15.1 Allen's test

- Arterial supply to the hand is normally from the radial and ulnar arteries.
- Used to determine if there is impaired collateral circulation to the hand.
- The patient holds their hand up and clenches their fist.
- Both the radial and ulnar arteries are occluded by compression.
- The patient is asked to open their fist, and pressure is released from the ulnar artery.
- Colour should return to the hand within 5s.

- Advance until flashback is seen.
- The syringe should self-fill in a pulsatile manner if in the artery.
- Remove the needle and apply pressure to the site until haemostasis is achieved (normally 3–5min).
- Air bubbles should be removed from the sample. The sample should be analysed immediately or placed on ice and analysed within 15min (to reduce oxygen consumption by white blood cells).

Complications

- Bleeding.
- Bruising.
- Vessel injury.
- Local thrombus.

Possible locations

Radial artery

The radial artery is more accessible and more comfortable for the patient; it is best palpated between the bony head of the distal radius and the tendon of the flexor carpi radialis, with the wrist dorsiflexed.

Brachial artery

The brachial artery is best palpated medial to the biceps tendon in the antecubital fossa, with the arm extended and the palm facing up. The needle is inserted just above the elbow crease.

Femoral artery

The femoral artery is best palpated just below the midpoint of the inguinal ligament, with the leg extended. The needle is inserted below the inguinal ligament at a 90° angle. A larger needle (e.g. 21G (green)) may be required. The needle should be inserted at a 60–90° angle to the skin. Pressure should be applied to the site for longer (5–15min).

Arterial line insertion

Indications

- Continuous monitoring of arterial BP in critically ill patients with haemodynamic instability.
- Repeated arterial blood sampling.

Contraindications

- Coagulopathy.
- Raynaud's phenomenon.
- Thromboangiitis obliterans.
- Advanced atherosclerosis.
- End arteries, such as the brachial artery, should be avoided.

Equipment required

- Gauze.
- Gloves.
- 70% isopropyl alcohol wipe.
- Sterile drapes.
- Arterial line kit (20G arterial catheter, 22G introducer needle, soft-tip wire, suture).

General technique

- Locate a palpable artery (e.g. radial or femoral).
- If radial, assess ulnar blood flow by using the Allen's test (see Box 15.1).
- If radial, position the hand in moderate dorsiflexion, with the palm facing up (to bring the artery closer to the skin).
- Clean the site with a sterile preparation solution and appropriately drape.
- Use sterile gloves.
- Infiltrate local anaesthetic (1% lidocaine) in the conscious patient.
- Palpate the artery with the non-dominant hand (1–2cm from the wrist between the bony head of the radius and flexor carpi radialis tendon).

Over-the-wire/Seldinger technique

- The catheter and needle are advanced towards the artery at a 30–45° angle (see Fig. 15.1A(a)) until blood return is seen (see Fig. 15.1A(b)).
- The catheter and needle are then advanced through the vessel a few millimetres further (see Fig. 15.1A(c)) to transfix the artery.
- The needle is removed (see Fig. 15.1A(d)).
- The catheter is withdrawn until pulsatile blood flow is seen (see Fig. 15.1A(e)).
- When pulsatile blood flow is seen, the wire is advanced into the vessel (see Fig. 15.1A(f)).
- The catheter is advanced into the vessel *over the wire* (see Fig. 15.1A(g)).
- While placing pressure over the artery, the wire is removed (see Fig. 15.1A(h)) and the catheter is connected to a transduction system.

Over-the-needle technique

- The catheter and needle are advanced towards the artery at a 30–45° angle (see Fig. 15.1B(a)) until blood return is seen (see Fig. 15.1B(b)).
- The catheter and needle are then advanced slightly further and the catheter/needle angle is lowered to 10–15° (see Fig. 15.1B(c)).

- The catheter is advanced into the vessel *over the needle* (see Fig. 15.1B(d)).
- Proximal pressure is applied to the artery; the needle is removed (see Fig. 15.1B(e)), and the catheter is connected to the transducer.

Final steps

- Secure the catheter in place by using suture or tape.
- Check perfusion to the hand after insertion of the arterial line and at frequent intervals.
- The line should be removed if there are any signs of vascular compromise or as early as possible after it is no longer needed.

Complications

- Local and systemic infection.
- Bleeding, haematoma, and bruising.
- Vascular complications: blood vessel injury, pseudoaneurysm, thromboembolism, and vasospasm.
- Arterial spasm may occur after multiple unsuccessful attempts at arterial catheterization. If this occurs, use an alternative site.
- There may be difficulty in passing a wire or catheter despite the return of pulsatile blood. Adjustment of the angle, and withdrawal or slight advance of the needle, may be helpful.

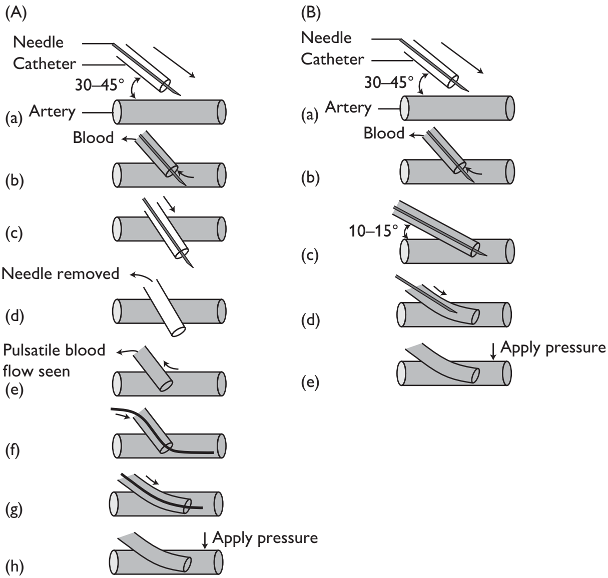
(A)
Needle
Catheter
30–45°
(a)
Artery
Blood
(b)
(c)
Needle removed
(d)
Pulsatile blood flow seen
(e)
(f)
(g)
Apply pressure
(h)
(B)
Needle
Catheter
30–45°
(a)
Artery
Blood
(b)
10–15°
(c)
(d)
Apply pressure
(e)

Fig. 15.1 Arterial line insertion techniques: (A) over-the-wire (Seldinger) technique; (B) over-the-needle or slide-off technique.

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Central line insertion

Indications

- Central venous pressure (CVP) monitoring.
- Haemodialysis.
- Administration of caustic medications.
- Emergency venous access.
- Access for transvenous pacing wire or pulmonary artery catheter.
- Need to deliver IV medications to a patient with difficult access.

Contraindications

- Infection at insertion site.
- Distorted anatomy or trauma.
- Current or intended thrombolysis.
- Coagulopathy.
- Uncooperative patient.

Equipment/personnel required

- Sterile dressing pack and gloves.
- 10mL and 5mL syringes with green (21G) and orange (25G) needles.
- Local anaesthetic (e.g. 2% lidocaine).
- Central line (e.g. 16G long Abbocath® or Seldinger catheter).
- Saline flush.
- Silk suture and needle.
- No. 11 scalpel blade.
- Sterile occlusive dressing (e.g. Tegaderm®).
- US machine (see Box 15.2).
- An additional person/assistant.

Risks

- Arterial puncture (remove and apply local pressure).
- Pneumothorax (insert chest drain or aspirate if required).
- Haemothorax.
- Chylothorax (mainly left subclavian lines).
- Infection (local, septicaemia, bacterial endocarditis).
- Brachial plexus or cervical root damage (overenthusiastic infiltration with local anaesthetic).
- Arrhythmias.

Use of ultrasound

- Traditional insertion methods use anatomical landmarks to determine vein position; these relationships are significantly variable.
- Failure and complication rates using landmark methods are significant, and therefore, serious complications may occur.
- *All internal jugular vein (IJV) central lines should be placed under US guidance*. However, additional training with this equipment is required.
- Advantages of this technique include:
  - Identification of the actual and relative vein position (see Fig. 15.4)
  - Identification of anatomical variations
  - Confirmation of target vein patency.

General technique

- Lie the patient supine (± head-down tilt).
- Perform a non-sterile US scan to assess vein patency/size.
- Clean the skin with iodine or chlorhexidine: from the angle of the jaw to the clavicle for IJV cannulation, and from the midline to the axilla for the subclavian approach.
- Use drapes to isolate the sterile field.
- Flush the lumen of the central line with saline.
- Identify landmarks (see ➔ Central line insertion: routes, pp. 704–5), and identify the vein on US.
- Infiltrate the skin and subcutaneous tissue with local anaesthetic.
- The introducer needle is inserted through the skin and advanced with gentle negative pressure on the syringe under US guidance.
- With the needle in the vein, check that you can aspirate blood freely. Immobilize the needle relative to the skin and mandible/clavicle.
- Remove the syringe and pass the guidewire into the vein; it should pass freely.
- Remove the needle, leaving the wire within the vein. Use a sterile swab to maintain gentle pressure over the site to prevent excessive bleeding.
- With a No. 11 blade, make a nick in the skin where the wire enters, to facilitate dilatation of the subcutaneous tissues. Pass the dilator over the wire and remove, leaving the wire *in situ*.
- Pass the central line over the wire into the vein. Remove the guidewire; flush the lumen with fresh saline, and close off to air.
- Suture the line in place, and cover the skin penetration site with a sterile occlusive dressing.

Complications

- Pneumothorax.
- Arterial puncture.
- Malposition.
- Infection.
- Thrombosis.
- Arrhythmia.

Box 15.2 Setting up ultrasound equipment

- Ensure that the display can be seen.
- The sheath is opened (operator) and gel squirted in (assistant). *A generous amount of gel ensures good contact and air-free coupling between the probe tip and the sheath. Too little may compromise image quality.*
- The probe and connecting cable are lowered into the sheath (assistant), which is then unrolled along them (operator).
- A rubber band secures the sheath to the probe.
- The sheath over the probe tip is smoothed out (wrinkles will degrade image quality).
- Apply liberal amounts of gel to the sheathed probe tip for good ultrasound transmission and ↑ patient comfort during movement.

Central line insertion: routes

- US guidance should be used for all techniques outlined.

Internal jugular vein route

Anatomical location

- The IJV runs just posterolateral to the carotid artery within the carotid sheath. It lies medial to the sternocleidomastoid muscle (SCM) in the upper part of the neck, between the two heads of the SCM in its medial portion, and enters the SCV near the medial border of the anterior scalene muscle (see Fig. 15.2).
- There are three basic approaches to IJV cannulation: medial to the SCM, between the two heads of the SCM, or lateral to the SCM. The approach used depends on the experience of the operator/institution.
- Locate the carotid artery between the sternal and clavicular heads of the SCM at the level of the thyroid cartilage; the IJV lies lateral and parallel to it.

Additions to the general technique

- Turn the patient's head away from the side you wish to cannulate.
- The introducer needle is advanced at 45° angle with gentle negative suction on the syringe, aiming for the ipsilateral nipple and guided by the US image.

Subclavicular route

Anatomical location

(See Fig. 15.3)

- The axillary vein becomes the SCV at the lateral border of the first rib and extends for 3–4cm just deep to the clavicle.
- The subclavian artery and brachial plexus lie posteriorly, separated from the vein by the scalenus anterior muscle.
- The phrenic nerve and internal mammary artery lie behind the medial portion of the SCV, and on the left lies the thoracic duct.

Additions to the general technique

- Select the point 1cm below the junction of the medial third and middle third of the clavicle. If possible, place a bag of saline between the scapulae to extend the spine.
- Infiltrate the skin and subcutaneous tissue and periosteum of the inferior border of the clavicle with local anaesthetic up to the hilt of the green (21G) needle, ensuring that it is not in a vein.
- Insert the introducer needle with a 10mL syringe, guiding gently under the clavicle. It is safest to initially hit the clavicle, and 'walk' the needle under it until the inferior border is just cleared. In this way, you keep the needle as superficial to the dome of the pleura as possible. Once underneath the clavicle, advance it slowly towards the contralateral sternoclavicular joint, aspirating as you advance.
- Once venous blood is obtained, rotate the bevel of the needle towards the heart. This encourages the guidewire to pass down the brachiocephalic vein rather than up the IJV.
- When removing the dilator, note the direction that it faces; it should be slightly curved downwards. If it is slightly curved upwards, then it is likely that the wire has passed up into the IJV. The wire may be

manipulated into the brachiocephalic vein under fluoroscopic control, but, if not available, it is safer to remove the wire and start again.

- A CXR is mandatory after subclavian or internal jugular line insertion, to exclude a pneumothorax and confirm satisfactory placement of the line.

Tips and pitfalls

- Venous blood is dark, and arterial blood is pulsatile and bright red!
- Once you locate the vein, take care not to release your fingers from the pulse; they may be distorting the anatomy, making access to the vein easier, and if released, it may prove difficult to relocate the vein.
- It is easier, and safer, to cannulate a central vein with the patient supine/head down; ↑ risk of air embolus if patient semi-recumbent.

Guidewire not passing

- The guidewire should pass easily into the vein.
- If there is resistance, remove the wire; check that the needle is still within the lumen, and try again.
- *Left IJV approach:* there are several acute bends to be negotiated. If the wire keeps passing down the wrong route, ask an assistant to hold the patient's arms out at 90°, or even above the patient's head.
- *Subclavicular route:* if there is difficulty, try advancing during the inspiratory and expiratory phases of the respiratory cycle.

Intubated patients

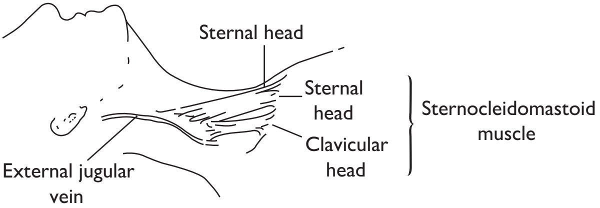
- It may be difficult to access the head of the bed. The anterior IJV approach may be easier (see Fig. 15.2) and may be done from the side of the bed (left side of the bed for right-handed operators, using the left hand to locate the pulse and the right hand to cannulate the vein).

Measuring the central venous pressure

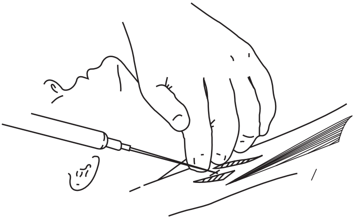
- When asked to see a patient with an abnormal central venous pressure reading, it is a good habit to always recheck the zero and the reading yourself.
- Always measure with the mid-axillary point as the zero reference. Sitting the patient up will drop the pressure (pooling in the veins).
- Fill the manometer line, being careful not to soak the cotton wool stopping. If this gets wet, it limits the free-fall of saline or dextrose in the manometer line.
- Look at the rate and character of the venous pressure. It should fall to its value quickly and swing with respiration.
- If it fails to fall quickly, consider whether the line is open (i.e. saline running in), or blocked with blood clot, is positional (up against the vessel wall—ask the patient to take some deep breaths), or arterial blood (blood tracks back up the line). Raise the whole drip-stand, and make sure that the level falls. If it falls when the whole stand Is elevated, it may be that the central venous pressure is very high.

Central line insertion landmarks

(a) Surface anatomy of external and internal jugular veins


Sternal head
Sternal head
Clavicular head
Sternocleidomastoid muscle
External jugular vein

(b) Anterior approach: the chin is in the midline and the skin puncture is over the sternal head of the SCM muscle



(c) Central approach: the chin is turned away and the skin puncture is between the two heads of the SCM muscle

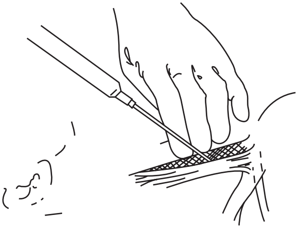


Fig. 15.2 Internal jugular vein cannulation.

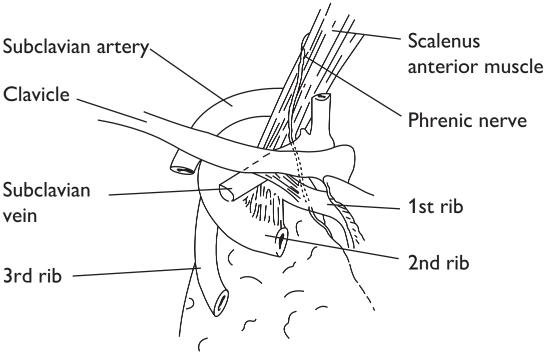

Subclavian artery
Clavicle
Subclavian vein
3rd rib
Scalenus anterior muscle
Phrenic nerve
1st rib
2nd rib

Fig. 15.3 The subclavian vein and surrounding structures.

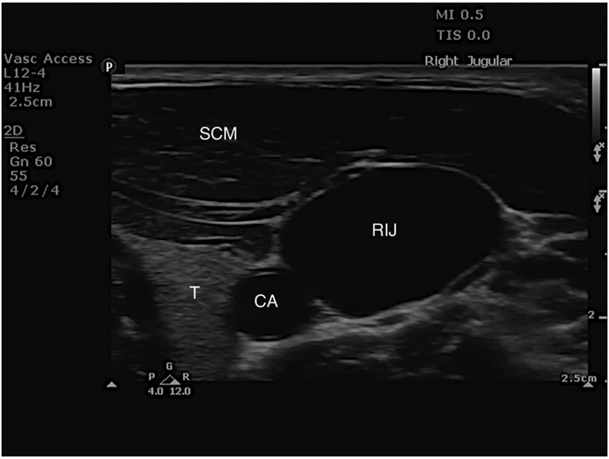

MI 0.5
TIS 0.0
Right Jugular
Vasc Access
L12-4
41Hz
2.5cm
2D
Res
Gn 60
55
4/2/4
P
SCM
RIJ
T
CA
G
P
R
4.0 12.0
2
2.5cm

Fig. 15.4 Ultrasound image showing the carotid artery and internal jugular vein.

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Pulmonary artery catheterization

- PA catheters (Swan–Ganz) allow measurement of several haemodynamic parameters that may aid in clinical decision-making in critically ill patients (assess RV and LV function, guide treatment, and provide prognostic information).
- A PA catheter itself is a diagnostic tool and has no therapeutic benefit. A meta-analysis has shown no benefit to mortality with its use.
- Careful and frequent clinical assessment should accompany measurements; PA catheterization should not delay treatment.

Indications

- Evaluation of PHT.
- CO measurement.
- Evaluation of complicated shock—measurement of CVP and CO (e.g. complicated MI).
- Assessment of fluid replacement and therapy effects (e.g. inotropes) in unstable/critically unwell patients.

Contraindications

- Active infection over insertion site.
- Right-sided VAD.
- Right-sided endocarditis.
- Right heart mass (e.g. tumour, thrombus).
- Severe coagulopathy/thrombocytopenia are a relative contraindication.

Equipment required

- Full resuscitation facilities should be available, and the patient's ECG should be continuously monitored.
- A bag of heparinized saline for flushing the catheter and a transducer set for pressure monitoring. (Check that your assistant is experienced in setting up the transducer system BEFORE you start.)
- An 8F introducer kit (pre-packaged kits contain the introducer sheath and all the equipment required for central venous cannulation).
- PA catheter: commonly a triple-lumen catheter that allows simultaneous measurement of RA pressure (proximal port) and PA pressure (distal port), and incorporates a thermistor for measurement of CO by thermodilution.
- Fluoroscopy is preferable, although not essential.

General technique

- Do not attempt this without supervision if you are inexperienced.
- Observe a strict aseptic technique.
- Insert the introducer sheath (at least 8F in size) into the IJV, SCV, or femoral vein in the standard way (see ➔ Central line insertion, pp. 702–3). Flush the sheath with saline, and secure to the skin with sutures.
- Flush all the lumens of the PA catheter, and attach the distal lumen to the pressure transducer. Check the transducer is zeroed (conventionally to the mid-axillary point). Check the integrity of the balloon by inflating and deflating it with the syringe provided (1–2 mL of air).

- Pass the tip of the PA catheter through the plastic sheath, keeping the sheath compressed. The catheter is easier to manipulate without the sheath over it; once in position, extend the sheath over the catheter to keep it sterile.
- With the balloon deflated, advance the tip of the catheter to 10–15cm from the right IJV/SCV, 15–20cm from the left. Check that the pressure tracing is typical of the RA pressure (see Fig. 15.4).
- Inflate the balloon and advance the catheter gently. The flow of blood will carry the catheter across the TV, through the RV and into the PA.
- Watch the ECG tracing whilst advancing the catheter. Runs of VT are often triggered when crossing the TV and through the RV. VT is usually self-limiting but should not be ignored. Deflate the balloon; pull back, and try again.
- As the tip passes into a distal branch of the PA, the balloon will not pass further—the wedge position—and the pressure tracing will change (see Fig. 15.4).
- Deflate the balloon and check that a typical PA tracing is obtained. If not, try flushing the catheter lumen, and if that fails, withdraw the catheter until the tip is within the PA and begin again.
- Reinflate the balloon slowly. If the PCWP is seen before the balloon is fully inflated, it suggests the tip has migrated further into the artery. Deflate the balloon; withdraw the catheter 1–2cm, and try again.
- When a stable position has been achieved, extend the plastic sheath over the catheter and secure it to the introducer sheath. Secure a coil of the catheter to the patient's chest to avoid inadvertent removal.
- Obtain a CXR to check the position of the catheter. The tip of the catheter should ideally be no more than 3–5cm from the midline.

Complications

- As with central lines (see ➔ Complications, p. 703).
- Ventricular arrhythmias—commonly when crossing the TV.
- RV mural thrombus.
- Air embolism from rupture balloon.
- Pulmonary infarction.
- Knots—these usually occur at the time of initial placement in patients where there has been difficulty in traversing the RV.
- Endocarditis—risks ↑ with the duration the catheter is left *in situ*.
- Damage to the PV or TV.
- PA rupture—damage may occur if the balloon is overinflated in a small branch, the balloon is inflated for long periods, or the catheter is advanced too far into the pulmonary system ('over-wedging'). Risk factors include MV disease (large 'v' wave confused with poor wedging), PHT, and multiple inflations or hyperinflations of the balloon. Haemoptysis is an early sign.

Pulmonary artery catheterization: tips and pitfalls

- Normal values are provided in Box 15.3, and a standard pressure trace is seen in Fig. 15.5.
- The catheter softens with time at body temperature and the catheter tip may migrate further into the PA branch. If the pressure tracing with the balloon deflated is ‘partially wedged’ (and flushing the catheter does not improve this), withdraw 1–2cm and reposition.
- Sometimes it is impossible to obtain a wedged trace. In this situation, one has to use the PA diastolic pressure as a guide. In health, there is 2–4mmHg difference between PA diastolic pressure and PCWP. Any condition that causes PHT (e.g. severe lung disease, acute respiratory distress syndrome (ARDS), long-standing valvular disease) will alter this relationship.
- If >15cm of catheter is advanced into the RV, without the tip entering the PA, this suggests the catheter is coiling in the RV. Deflate the balloon, and withdraw the catheter into the RA; reinflate the balloon, and try again by using clockwise torque while advancing in the ventricle or by flushing the catheter with cold saline to stiffen the plastic. If this fails repeatedly, try under fluoroscopic guidance.
- If the pressure tracing flattens and then continues to rise when you inflate the balloon, you have ‘overwedged’. Deflate the balloon; pull the catheter back 1–2cm, and start again.

Things to never do with a pulmonary artery catheter

- Never withdraw the catheter with the balloon inflated.
- Never advance the catheter with the balloon deflated.
- Never inject liquid into the balloon.
- Never leave the catheter with the balloon inflated, as pulmonary infarction may occur.

Special circumstances

- *Valvular lesions, VSDs, prosthetic valves, and pacemakers:* if these are present, seek cardiology advice. The risk of bacterial endocarditis may be sufficient that a PA catheter may be more detrimental than beneficial.
- *Positive end-expiratory pressure (PEEP):* measurement and interpretation of PCWP in patients on PEEP depends on the position of the catheter. Ensure the catheter is below the level of the LA on a lateral CXR. Removing PEEP during measurement causes marked fluctuations in haemodynamics and oxygenation, and the pressures do not reflect the state once back on the ventilator.

Box 15.3 Normal values of right heart pressures and flows

Right atrial pressure	0–8mmHg
Right ventricle	
• Systolic	15–30mmHg
• End diastolic	0–8mmHg
Pulmonary artery	
• Systolic/diastolic	9–16mmHg
• Mean	15–30/4–12mmHg
Pulmonary capillary wedge pressure	2–10mmHg
Cardiac index	2.8–4.2L/min/m^2

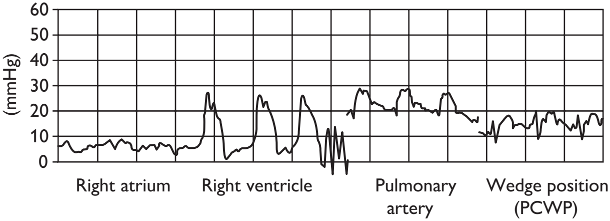

Fig. 15.5 Pressure tracings during pulmonary artery catheterization.

Temporary pacing: ventricular

- Temporary pacing wires allow for control of bradyarrhythmias in an emergency setting.
- Their use has declined and they are reserved for situations where it is felt that a permanent pacing system is not required long term.
- Insertion of temporary pacing wires after MI has ↓ significantly with primary revascularization.
- The most commonly used pacing mode and the mode of choice for life-threatening bradyarrhythmias is ventricular demand pacing, with a single bipolar wire positioned in the RV.

Indications

- Bradycardia with haemodynamic compromise for a potentially reversible cause (see ➔ Bradycardia: emergency management, pp. 132–3 and Box 3.2).
- Ventricular arrhythmia suppression.
- Overdrive pacing/tachyarrhythmia termination (e.g. recurrent VT).
- Preoperative prophylactic procedure in those at high risk of bradycardia/asystole perioperatively.
- TAVI.
- Box change of a permanent system in a pacing-dependent patient.
- Post-cardiac surgery (see Box 15.4).

Box 15.4 Epicardial temporary pacing

- Following cardiac surgery, patients may have *epicardial wires* (attached to the pericardial surface of the heart) left in for up to 1 week in case of post-operative bradyarrhythmia.
- These are used in the same way as transvenous pacing wires, but the threshold may be higher.

Contraindications

- Coagulopathy.
- Bacteraemia or systemic infection.
- Intracardiac thrombus.

Equipment required

- Temporary pacing wire.
- Introducer sheath.
- Temporary pacing box.
- Sterile drapes.
- Trolley as for central line insertion, with chlorhexidine for skin cleaning, dressing pack, sterile drapes, local anaesthetic (lidocaine 2%), No. 11 blade, and sutures.

General technique

- *Cannulate a central vein:* the wire is easiest to manipulate via the right internal jugular (RIJ) approach, but it is more comfortable for the patient via the right SCV. The left internal jugular (LIJ) approach is best avoided, as there are many acute bends to negotiate and it is difficult to achieve a stable position. Avoid the left subclavicular area—the preferred area for PPM insertion and should be kept 'virgin' if possible. The femoral vein may be used (incidence of deep vein thrombosis (DVT) and infection is high).
- *Insert a sheath* (similar to that for PA catheterization), through which the pacing wire can be fed. Pacing wires are commonly 5F or 6F, and a sheath at least one size larger is necessary.
- Pass the wire through the introducer sheath, and advance it into the upper RA (see Fig. 15.5).
- Advance the wire, with the tip pointing towards the RV; it may cross the TV easily.
- Advance and rotate the wire, so that the tip points inferiorly as close to the RV apex as possible.
- Connect the wire to the pacing box and check the threshold. Ventricular pacing thresholds should be <1.0V, but a threshold of up to 1.5V is acceptable if another stable position cannot be achieved.
- Check for positional stability. With the box pacing at a rate higher than the intrinsic HR, ask the patient to take some deep breaths, cough forcefully, and sniff. Watch for failure of capture, and if this occurs, reposition the wire.
- Set the output to 3V and the box on 'demand'. If the patient is in SR and has adequate BP, set the box rate to 10/min below the patient's rate. If there is CHB or bradycardia, set the rate at 70–80/min.
- Suture the sheath and wire securely to the skin. Loop the rest of the wire and fix to the patient's skin with adhesive dressing.
- When the patient returns to the ward, obtain a CXR to confirm satisfactory positioning of the wire and to exclude a pneumothorax.

Tips and pitfalls

- If the wire fails to cross the TV, point the tip towards the lateral wall of the atrium and form a loop. Rotate the wire and the loop should fall across the TV into the ventricle.
- If the wire does not rotate down to the apex easily, it may be because you are in the coronary sinus rather than in the RV (the tip of the wire points to the left shoulder). Withdraw the wire and recross the TV.
- Check the screening equipment and defibrillator are working.
- Check the type of pacing wire—atrial wires have a preformed 'J' that allows easy placement in the atrium or appendage, and is very difficult to manipulate into a satisfactory position in the ventricle. Ventricular pacing wires have a more open, gentle 'J'.
- Check the pacing box (single vs dual or sequential pacing box) and leads to attach to the wire(s). Familiarize yourself with the controls on the box—you may need to connect up in a hurry if the patient's intrinsic rhythm slows further.

Temporary pacing: complications

- Complications associated with central line insertion.
- Infection.
- Pneumothorax.

Ventricular ectopics or tachycardia

- NSVT is common as the wire crosses the TV (especially in patients on an isoprenaline infusion) and does not require treatment.
- Try to avoid long runs of VT and, if necessary, withdraw the wire into the atrium and wait until the rhythm has settled.
- If ectopics persist after the wire is positioned, try adjusting the slack in the wire in the region of the TV (either more or less).
- Pacing the RVOT can provoke runs of VT.

Failure to pace and/or sense

- It is difficult to get thresholds of <1V in those with extensive MI (especially of the inferior wall) or cardiomyopathy, or those on class I antiarrhythmics. Accept a slightly higher value if the position is otherwise satisfactory.
- If the position of the wire appears satisfactory and yet the pacing thresholds are high, the wire may be in the left hepatic vein. Pull the wire back into the atrium and try again, looking specifically for ventricular ectopics as the wire crosses the TV.
- The threshold often doubles in first few days due to endocardial oedema.
- ↑ the pacing output of the box.
- Check all connections of the wire and the battery of the box.
- Wire displacement is the most likely reason for sudden device failure. Try moving the patient to the left lateral position until arrangements can be made to reposition the wire.

Perforation

- Typically, perforation occurs in the RV.
- A pericardial rub may be present in the absence of perforation (especially post-MI).
- *Presentation:* pericardial chest pain, ↑ breathlessness, falling BP, enlarged cardiac silhouette on CXR, signs of cardiac tamponade, left diaphragmatic pacing at low output.
- *Management:* if there are signs of cardiac tamponade, arrange for urgent echocardiography and reposition the wire. Treat the tamponade. Monitor the patient carefully over the next few days, with repeat echocardiography to detect incipient cardiac tamponade.

Diaphragmatic pacing

- High-output pacing (10V), even with a satisfactory position of the ventricular lead, may cause pacing of the left hemidiaphragm. At low voltages, this suggests perforation (see ➔ Perforation above).
- Right hemidiaphragm pacing may be seen with atrial pacing and stimulation of the right phrenic nerve.
- Reposition the wire if symptomatic (painful twitching, dyspnoea).

Temporary pacing: other

Temporary atrial pacing

- Temporary atrial pacing is rarely used in modern practice.
- Occasionally used for overdrive pacing of the atria.
- The technique of inserting an atrial temporary wire is similar to that of ventricular pacing (see Fig. 15.6).
- Advance the atrial wire until the 'J' is reformed in the RA.
- Rotate the wire and withdraw slightly to position the tip in the RA appendage. Aim for a threshold of <1.5V.

Atrioventricular sequential pacing

- In critically ill patients with impaired cardiac pump function and symptomatic bradycardia (especially with RV infarction), the CO may be ↑ by up to 20% by maintaining AV synchrony.
- This requires two pacing leads, one atrial and one ventricular, and a dual pacing box.
- Use of two temporary pacing wires was previously considered. However, in modern practice, most patients would receive a dual-chamber pacemaker system instead.

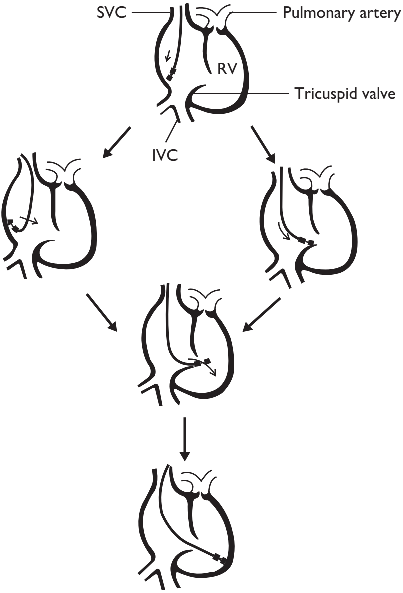

Fig. 15.6 Insertion of a ventricular pacing wire (see text for details).

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Pericardial aspiration

Indications

- Cardiac tamponade.
- Diagnosis of pericardial effusion.
- Palliative removal of pericardial fluid.

Contraindications

- Coagulopathy (not a contraindication in cardiac tamponade).

Equipment required

Pre-prepared pericardiocentesis sets may be available.

- Trolley as for central line insertion, with chlorhexidine for skin cleaning, dressing pack, sterile drapes, local anaesthetic (lidocaine 2%), syringes (including 50mL), needles (25G and 22G), No. 11 blade, and silk sutures.
- Pericardiocentesis needle (15cm, 18G) or similar Wallace cannula.
- J guidewire (≥80cm, 0.035 diameter).
- Dilators (up to 7F).
- Pigtail catheter (≥60cm with multiple side holes).
- Drainage bag and connectors.
- Facilities for fluoroscopy and echocardiographic screening.

General technique (subcostal)

- Position the patient at 30°, allowing the effusion to pool inferiorly.
- Lightly sedate the patient (e.g. midazolam 2.5–7.5mg IV), if necessary. Caution—may drop BP if the patient is compromised by effusion.
- Use a sterile technique to clean the skin from mid chest to mid abdomen, and put sterile drapes on the patient.
- Confirm the location of the pericardial effusion by using TTE guidance.
- Infiltrate the skin/subcutaneous tissues with lidocaine, starting 1–1.5cm below the xiphisternum, just to the left of the midline. Aim for the left shoulder and remain close to the rib cartilage's inferior border.
- The pericardiocentesis needle is introduced into the angle between the xiphisternum and the left costal margin angled at 30°. Advance slowly under TTE guidance, aspirating gently, and then injecting more lidocaine every few millimetres, aiming for the left shoulder.
- As the parietal pericardium is pierced, you may feel a 'give' and fluid will be aspirated. The needle and/or injected agitated saline can be visualized on TTE to confirm the location.
- Remove the syringe and introduce the guidewire through the needle.
- Screen to check the guidewire position. It should loop within the cardiac silhouette and not advance into the SVC or PA.
- Remove the needle, leaving the wire in place. Enlarge the skin incision slightly by using the blade, and dilate the track.
- Insert the pigtail over the wire and remove the wire.
- Take required specimens (see ➔ Pericardial fluid analysis, p. 313).
- Aspirate to dryness; watch the patient carefully. Resolution of the effusion can be visualized on TTE. Symptoms/haemodynamics often improve with removal of ~100mL of pericardial fluid.

- If the fluid is heavily bloodstained, remove fluid cautiously—if the pigtail is in the RV, may cause circulatory collapse (see Box 15.5).
- Leave on free drainage and attached to the drainage bag.
- Suture the catheter to the skin securely, and cover with a sterile dressing.

Complications

- Penetration of a cardiac chamber (usually RV).
- Laceration of an epicardial vessel.
- Arrhythmia (atrial as wire is advanced; ventricular if the RV is penetrated).
- Pneumothorax.
- Perforation of abdominal viscus (liver, stomach, colon).
- Infection.

Aftercare

- Closely observe the patient for recurrent tamponade and repeat TTE.
- Discontinue anticoagulants.
- Remove the drain after 24h or when the drainage stops.
- Consider the need for surgery (drainage, biopsy, or pericardial window) or specific therapy (chemotherapy if malignant, antimicrobials if bacterial, dialysis if renal failure, etc.).

Tips and pitfalls

- *Needle touches the epicardial surface:* you may feel a 'ticking' sensation transmitted down the needle. Withdraw a few millimetres; angulate more superficially and cautiously advance, aspirating as you go.
- *If you do not enter the effusion, and the heart is not encountered:* withdraw the needle slightly and advance again, aiming slightly deeper, but still towards the left shoulder. If this fails, try again, aiming more medially (mid-clavicular point or even the suprasternal notch). Consider an apical approach if TTE confirms sufficient apical fluid.
- If available, *intrathoracic ECG* can be monitored by a lead attached to the needle as it is advanced. Penetration of the myocardium causes ST-segment elevation, suggesting the needle is too advanced.
- *Difficulty in inserting the pigtail:* may be due to insufficient tract dilatation (use a larger dilator). Putting gentle traction on the wire while pushing the catheter may help; take care not to pull the wire out.

Box 15.5 Haemorrhagic effusion vs blood

- Compare Hb of the pericardial fluid to venous blood Hb.
- Place fluid in a clean container—blood will clot; haemorrhagic effusion will not as it is defibrinated.
- Confirm the position of the needle by first withdrawing some fluid and then injecting 10–20mL of contrast; using fluoroscopy, see if the contrast stays within the cardiac silhouette.
- Using TTE guidance, inject 10mL of saline into the needle, looking for 'microbubble contrast' in the cavity containing the needle tip. Injecting 20mL of saline rapidly into a peripheral vein will produce 'contrast' in the RA and RV, allowing them to be distinguished.
- Connect a pressure line to the needle; a characteristic waveform will confirm penetration of the RV.

Direct current cardioversion

Indications

- *Emergency:* haemodynamically compromised tachyarrhythmia, VT with pulse, SVT not responding to other treatment.
- *Elective:* symptomatic AF despite appropriate rate control.

Relative contraindications

- Digoxin toxicity.
- Electrolyte disturbance (↓ Na^+, ↓ K^+, ↓ Ca^{2+}, ↓ Mg^{2+}, acidosis).
- Inadequate anticoagulation and chronic AF.

Required equipment/staff

- Defibrillator.
- Nursing staff to assist.
- May require additional staff for anaesthesia or sedation.

General technique

- Obtain informed consent from the patient.
- Check electrolytes are in the normal range and the patient is not thyrotoxic.
- Confirm the patient has been appropriately anticoagulated for 4 weeks prior to DCCV if elective for AF (or AF has started within the last 24h). If on warfarin, has the INR been >2.0 throughout?
- Confirm rhythm on ECG—DCCV will not correct sinus tachycardia.
- Ideally the patient should be nil by mouth for 6h prior to DCCV.
- Obtain peripheral IV access.
- Attach the patient to the defibrillator (see Box 15.7 for pad positioning).
- ECG electrodes should be placed to allow transcutaneous pacing if significant bradycardia/heart block after cardioversion.
- Sedate the patient with either propofol (if anaesthetist present) or midazolam (2.5–5mg IV).
- Select energy (see Box 15.6) and synchronize the defibrillator.
- Once the patient is appropriately sedated, ensure no one is touching the bed; remove any oxygen, and deliver a single shock.
- If unsuccessful, check pad position; consider increasing energy (see Box 15.7), and repeat. Attempt a maximum of three shocks.
- If successful, repeat an ECG and monitor until sedation resolves. Patients should be accompanied by someone if being discharged.

Complications

- Asystole/bradycardias.
- VF.
- Thromboembolism.
- Transient hypotension.
- Skin burns.
- Aspiration pneumonitis.

Tips and pitfalls

- If sinus pause/sinus arrest seen following defibrillation, do not undertake further shocks if arrhythmia recurs unless it is an emergency.
- Consider altering pad position if initial shock is unsuccessful.

- Avoid oversedation with midazolam by giving in small boluses (e.g. 1–2mg). Peak effect is seen at 5–10min—it is easy to oversedate if boluses are given without a sufficient gap between them.

Anticoagulation

- The risk of thromboembolism in patients with chronic AF or DCM is 0–7%, depending on the underlying risk factors (CHA_2DS_2-VASc score; see ➔ Atrial fibrillation: stroke risk and anticoagulation, pp. 160–1).
- Anticoagulate at-risk patients with warfarin/DOAC for ≥4 weeks.
- For recent-onset AF (<24h), anticoagulate with LMWH prior to DC shock.
- If AF duration >24h, but DCCV required urgently, should have TOE to exclude thrombus (unless life-threatening emergency).
- If there is thrombus, anticoagulate with warfarin/DOAC as above.
- The risk of systemic embolism with cardioversion of other tachyarrhythmias is very low, provided there is no ventricular thrombus, since the coordinated atrial activity prevents clot formation. Routine anticoagulation is not necessary, but we would recommend heparin before DCCV. The atria are often mechanically stationary for several hours after shock, even with coordinated electrical depolarization.
- After successful cardioversion, if the patient is anticoagulated, continue for at least 4 weeks. Consider indefinite anticoagulation if warranted by the CHA_2DS_2-VASc score or other factors.

Box 15.6 Suggested initial energies for DC shock for elective cardioversion

Sustained ventricular tachycardia	200J	Synchronized
Atrial fibrillation	50–100J	Synchronized
Atrial flutter	50J	Synchronized
Other supraventricular tachycardias	50J	Synchronized

- If the initial shock is unsuccessful, ↑ the energy (50, 100, 200J) and repeat.
- If still unsuccessful, consider changing paddle position and try 200J again. It is inappropriate to persist further with elective DCCV.

Box 15.7 Pad placement for DC cardioversion

- Most centres now use 'hands-free' adhesive pads for DCCV.
- If using traditional handheld paddles, conductive gel pads should be placed between the paddles and the skin.
- Position one just to the right of the sternum, and the other to the left of the left nipple (anterior mid-axillary line).
- Alternatively, place one anteriorly just left of the sternum, and one posteriorly to the left of midline. There is some evidence that the anteroposterior position is superior for atrial fibrillation.

DC cardioversion: special situations

Pregnancy

- DC shock during pregnancy appears to be safe but should only be considered after careful discussion with the obstetrics team.
- Auscultate the fetal heart before and after cardioversion.
- If possible, the fetal ECG should be monitored.

Pacemakers

- There is a danger of damage to the pacemaker generator box or the junction at the tip of the pacing wire(s) and endocardium.
- Position the paddles in the anteroposterior position, as this is theoretically safer.
- Facilities for backup pacing (external or transvenous) should be available.
- Check the pacemaker post-cardioversion—both early and late problems have been reported.

Implantable cardioverter–defibrillators

- Cardioversion can be undertaken through the device.
- In patients with ICDs, discuss with the pacing department about undertaking the procedure through the device.

Congenital heart disease

- These situations can be difficult and deteriorate quickly.
- Early discussion with adult CHD specialists is recommended.

For further details, ➔ Tachyarrhythmias, p. 386.

Intra-aortic balloon counterpulsation

Indications

- Acute severe MR.
- Acute VSD.
- Preoperative (ostial left coronary stenosis).
- Weaning from cardiopulmonary bypass.
- Occasionally used for cardiogenic shock post-MI; however, no evidence of improved mortality.

Rarely

- Treatment of ventricular arrhythmias post-MI not controlled by antiarrhythmic therapy.
- UA (as a bridge to CABG).

Contraindications

- AR.
- Bleeding diathesis.
- Aortic dissection.
- Severe aorto-iliac atheroma.
- DCM (if not a cardiac transplant candidate).

Principles

- The device consists of a catheter with a balloon (40mL size) at its tip, which is positioned in the descending thoracic aorta.
- The balloon inflation/deflation is synchronized to the ECG.
- The balloon should inflate just after the dicrotic notch (in diastole), thereby ↑ pressure in the aortic root and ↑ coronary perfusion.
- The balloon deflates just before ventricular systole, thereby ↓ afterload and improving LV performance (see Fig.15.7).
- The intra-aortic balloon cannot assist the patient in asystole or VF; it requires a minimum cardiac index of 1.2–1.4L/min/m^2, often necessitating additional inotropes.
- Box 15.8 outlines the physiological effects of IABP.

Box 15.8 Physiological effects of counterpulsation

- ↑ coronary perfusion in diastole
- Reduced left ventricular end-diastolic pressure
- Reduced myocardial oxygen consumption
- ↑ cerebral and peripheral blood flow

Balloon insertion

- Previous experience is essential.
- Formerly, a cut-down to the femoral artery was required, but newer balloons come equipped with a sheath and are introduced percutaneously.
- Using fluoroscopy, the balloon is positioned in the descending thoracic aorta, with the tip below the origin of the left subclavian artery.
- Fully anticoagulate the patient with IV heparin.

- Some units routinely give IV antibiotics (flucloxacillin) to cover against *Staphylococcus* infection.

Triggering and timing

The balloon pump may be triggered either from the patient's ECG (R wave) or from the arterial pressure waveform. Slide switches on the pump allow precise timing of inflation and deflation during the cardiac cycle. Set the pump to 1:2, to allow you to see the effects of augmentation on alternate beats (see Figs. 15.7 and 15.8).

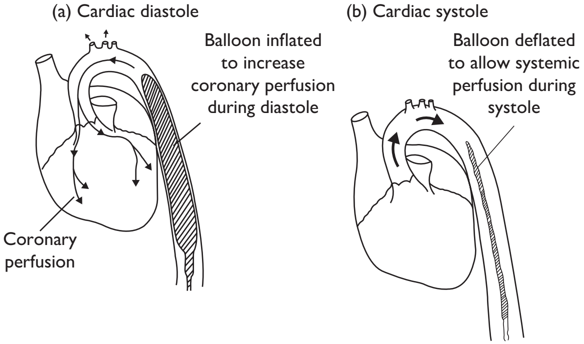
(a) Cardiac diastole
Balloon inflated to increase coronary perfusion during diastole
Coronary perfusion
(b) Cardiac systole
Balloon deflated to allow systemic perfusion during systole

Fig. 15.7 Intra-aortic balloon counterpulsation.

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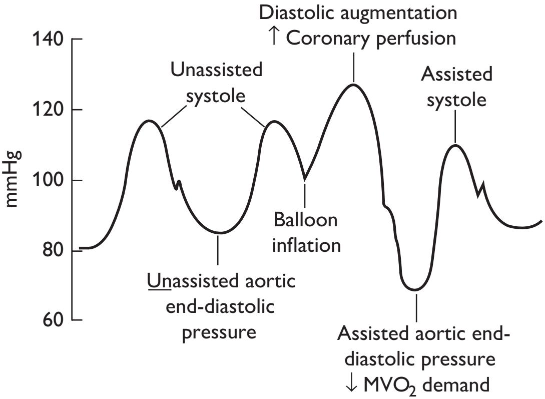

Fig. 15.8 Arterial waveform variations during intra-aortic balloon pump therapy. MVO$_2$, myocardial oxygen consumption.

Intra-aortic balloon counterpulsation: removal and complications

Intra-aortic balloon pump removal

- The patient may be progressively weaned by gradually reducing the counterpulsation ratio (1:2, 1:4, 1:8, etc.) and/or reducing the balloon volume and checking that the patient's BP remains stable.
- Stop the heparin infusion and wait for the ACT to fall to <150s (APTT <1.5 times normal).
- Using a 50mL syringe, have an assistant apply negative pressure to the balloon.
- Pull the balloon down until it abuts the sheath; do not attempt to pull the balloon into the sheath.
- Withdraw both the balloon and sheath, and apply firm pressure on the femoral puncture site for at least 30min or until bleeding is controlled.

Complications

- Aortic dissection.
- Thrombocytopenia.
- Arterial perforation.
- Peripheral embolism.
- Limb ischaemia.
- Balloon rupture.

Troubleshooting

- Seek help from an expert! There is usually an on-call cardiac perfusionist or technician, senior cardiac physician, or surgeon.
- Counterpulsation is inefficient with HR of over 130bpm. Consider antiarrhythmics or 1:2 augmentation instead.
- *Triggering and timing:* for ECG triggering, select a lead with the most pronounced R wave; ensure that the pump is set to trigger from the ECG, not pressure; PPMs may interfere with triggering—select a lead with a negative and the smallest pacing artefact (see also Fig. 15.9). Alternatively, set the pump to be triggered from the external pacing device. A good arterial waveform is required for pressure triggering; the timing will vary slightly, depending on the location of the arterial line (slightly earlier for radial artery line; cf. femoral artery line). Be guided by the haemodynamic effects of balloon inflation and deflation rather than by the precise value of the delay.
- *Limb ischaemia:* this is exacerbated by poor CO, adrenaline, noradrenaline, and peripheral vascular disease. Wean off and remove the balloon.
- *Thrombocytopenia:* commonly seen; does not require transfusion unless there is overt bleeding, and it returns to normal once the balloon is removed. Consider prostacyclin infusion if platelet counts fall below 100×10^9/L.

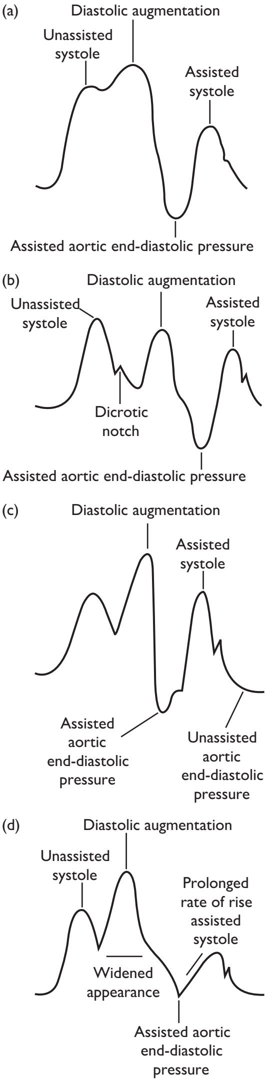
(a)
Diastolic augmentation
Unassisted systole
Assisted systole
Assisted aortic end-diastolic pressure
(b)
Diastolic augmentation
Unassisted systole
Assisted systole
Dicrotic notch
Assisted aortic end-diastolic pressure
(c)
Diastolic augmentation
Assisted systole
Assisted aortic end-diastolic pressure
Unassisted aortic end-diastolic pressure
(d)
Diastolic augmentation
Unassisted systole
Prolonged rate of rise assisted systole
Widened appearance
Assisted aortic end-diastolic pressure

Fig. 15.9 Timing errors. (a) Early inflation; (b) late inflation; (c) early deflation; (d) late deflation. IAB, intra-aortic balloon; LVEDV, left ventricular end-diastolic volume; LVEDP, left ventricular end-diastolic pressure; MVO_2, myocardial oxygen consumption.

Needlestick injuries

Occupational exposures to bloodborne viruses (BBVs) in healthcare workers can be divided into two groups: percutaneous (needlestick) and mucocutaneous (through broken skin or via splashes into the eyes). High-risk body fluids include blood, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid, amniotic fluid, human breast milk, cerebrospinal fluid, saliva (in dentistry), semen, vaginal secretions, and unfixed tissues and organs, as well as vomit, faeces, and urine when contaminated with blood. The major pathogens associated with needlestick injuries and mucocutaneous exposures are:

- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- HIV.

Occupational exposures to BBVs can be caused by:

- Not properly disposing of used needles
- Recapping needles
- Not using protective equipment (e.g. eye protection).

Prevention

Assume that every patient is potentially infected with a bloodborne infection. The same precautions should be taken for every patient and every procedure.

- Cover skin cuts and abrasions with waterproof dressings.
- Never recap needles or pass sharps hand to hand.
- Always dispose of used needles promptly in sharps disposal.
- Never leave sharps to be cleared up by others.
- Use eye protection. Ordinary spectacles offer inadequate protection. Use safety glasses that fit over spectacles.
- Double gloving: in case of needlestick injuries, 80% of visible blood can be removed by latex in a surgical glove. With double gloving, the inner glove will remove a further 80% of the remaining blood on the needle.

Management of exposure incidents

- If the mouth or eyes are involved, wash thoroughly with water.
- If the skin is punctured, let the wound bleed and wash it with soap or chlorhexidine and running water. Avoid scrubbing or sucking.
- Report to the occupational health department to arrange immediate assessment or, if out of hours, attend the emergency department in accordance with the local policy.

Assessment of risk of bloodborne virus transmission

Estimated seroconversion risks are:

- *Hepatitis B:* 30% for percutaneous exposure of a non-immune individual to HBsAg- and HBeAg-positive source.
- *Hepatitis C:* 1.9% for percutaneous exposure to HCV-infected blood with detectable HCV RNA.
- *HIV:* 0.3% for percutaneous exposure to HIV-infected blood.

Factors increasing the risk following injury include:

- Percutaneous injury, which is higher risk than mucous membrane or broken skin exposure
- Injury with a device directly from a source patient's artery/vein

- Injury from a hollow-bore and wide-gauge needle
- Deep injury
- Visible blood on the device
- High HIV viral load or HBeAg in the source patient
- Staff member inadequately immunized against hepatitis B.

Approaching source patients for bloodborne virus testing

- Due to the sensitivity of the issue, the source patient should not be approached by the exposed member of staff.
- Occupational health (or the emergency department if out of hours) will arrange this test in accordance with local policies.

Post-exposure prophylaxis for HIV

Risk assessment and follow-up are carried out by occupational health (the emergency department if out of hours). If the risk of infection is considered to be significant, post-exposure prophylaxis (PEP) should be started, ideally within an hour and certainly within 72h. Most hospitals recommend three agents:

- Zidovudine and lamivudine (co-administered as Combivir®, one tablet bd) or tenofovir/emtricitabine.
- A protease inhibitor (e.g. ritonavir-boosted lopinavir).

PEP therapy is associated with significant side effects. Initial discussion and subsequent follow-up should be with a clinician experienced in the use of these agents. If the ‘donor’ is known to be HIV-positive, ask about their antiretroviral therapy history, as this may alter the choice of drugs. Where possible, the ‘donor’ in such an injury should be encouraged to test for HIV to allow PEP therapy to be stopped.

Post-exposure prophylaxis for hepatitis B virus

If the patient has been vaccinated at least twice with hepatitis B vaccine and is known to be a responder (anti-HBS >10IU/mL), they should be given a booster injection, with a second dose 1 month later. For patients who have not been vaccinated or are known to be non-responders, they should be given an immediate injection of hepatitis B immunoglobulin (HBIG) and commence an accelerated course of hepatitis B vaccination, or have a booster dose if previously immunized.

Post-exposure prophylaxis for hepatitis C virus

Although there is no vaccine or effective PEP against hepatitis C, evidence suggests that early treatment with high-dose interferon can result in viral clearance in >90% of recently infected individuals. This emphasizes the importance of close and timely follow-up of exposed workers. Therefore, all individuals exposed to HCV should be tested for HCV antibodies at the time of exposure, and at 6–12 weeks and 26 weeks.

Chapter 16

Eponymous syndromes

Syndromes are listed in alphabetical order:

A–B *730*
C–F *732*
H–L *734*
M–T *736*
W *738*

A–B

Aase syndrome

A triad of congenital anaemia, triphalangeal thumbs, and ventricular septal defect (VSD). Autosomal recessive (AuR) inherited disorder; the genetic basis is unknown.

Cardiac manifestations: VSD.

Also known as: Aase–Smith syndrome.

Adams–Stokes syncope

(See ➲ Stokes–Adams syndrome, p. 737)

Alfidi’s syndrome

Hypertension resulting from occlusion of the coeliac axis, leading to diversion of collateral blood flow from the right renal artery and superior mesenteric artery. Also leads to chronic mesenteric ischaemia.

Cardiac manifestations: hypertension.

Also known as: renal–splanchnic steal syndrome.

Andersen syndrome

A form of long QT syndrome. Presents with a triad of periodic paralysis, ventricular tachyarrhythmias, and dysmorphic features (hypertelorism, micrognathia, low-set ears, and high-arched or cleft palate, short stature, scoliosis, syndactyly, and clinodactyly). Periodic paralysis can be associated with hyper-, hypo-, or normokalaemia. An autosomal dominant (AuD) condition associated with mutations in the *KCNJ2* gene encoding the inward-rectifying potassium ion channel Kir2.1.

Cardiac manifestations: long QT, ventricular arrhythmias.

Also known as: Andersen–Tawil syndrome, long QT syndrome 7.

Anderson–Fabry disease

(See ➲ Fabry disease, p. 733)

Barlow syndrome

A familial form of mitral valve prolapse, which is sometimes AuD inherited. A genetically heterogeneous syndrome, characterized by ‘billowing’ of one or both of the mitral valve leaflets into the left atrium during systole. There is a mid-systolic click and a late/pansystolic murmur; 20% are asymptomatic. Women are twice as commonly affected.

Cardiac manifestations: mitral valve prolapse.

Also known as: mitral valve prolapse syndrome, billowing mitral leaflet syndrome.

Barth syndrome

An X-linked mutation of the *TAZ* gene, leading to dilated cardiomyopathy, skeletal myopathy, short stature, and neutropenia. 3-methylglutaconic acid excretion in the urine has been observed; however, the concentration in the blood or urine does not correlate with clinical severity.

Cardiac manifestations: dilated cardiomyopathy, heart failure.

Also known as: 3-methylglutaconic aciduria type II, X-linked endocardial fibroelastosis.

Beemer lethal malformation syndrome

A lethal syndrome of a double-outlet right ventricle (RV), hydrocephalus, dense bones, thrombocytopenia, and abnormal nasal development. Only two cases worldwide have been reported.

Cardiac manifestations: double-outlet RV.

Also known as: Beemer–Ertbruggen syndrome.

Bland–Garland–White syndrome

A congenital condition featuring an anomalous origin of the left coronary artery arising from the pulmonary artery, resulting in myocardial ischaemia. Affected infants typically present with congestive heart failure within the first 1–2 months of life (dyspnoea and failure to thrive). Definitive treatment involves surgical reimplantation of the left coronary artery or bypass grafting.

Cardiac manifestations: anomalous coronary artery origin, heart failure.

Also known as: anomalous left coronary artery from the pulmonary artery (ALCAPA), White–Garland syndrome.

Bouillaud's syndrome

Eponym for rheumatic fever. Bouillaud was the first to emphasize the importance of cardiac involvement in the acute phase of the disease.

Cardiac manifestations: pericarditis, myocarditis, pancarditis.

Also known as: rheumatic fever.

Bourneville–Pringle disease

Hamartomas of the heart and kidney associated with epilepsy, learning difficulties, cerebral cortical hamartomas, and adenoma sebaceum. It is inherited in an AuD manner. Renal cysts or carcinomas may occur. Results from mutations in the *TSC1* or *TSC2* gene.

Cardiac manifestations: outflow tract obstruction, arrhythmia.

Also known as: tuberous sclerosis.

Bradbury–Eggleston syndrome

An idiopathic disorder of autonomic failure characterized by orthostatic hypotension, with more widespread manifestations of thermoregulatory, bowel, bladder, and sexual function disturbances.

Cardiac manifestations: syncope.

Also known as: pure autonomic failure.

Brugada's syndrome

One of the principal causes of sudden cardiac death (SCD) in young adults without structural heart disease. Secondary to an *SCN5A* mutation on chromosome 3, inherited in an AuD fashion. Results in sodium ion channel malfunction, leading to initiation and perpetuation of ventricular arrhythmias. Clinically, there is right bundle branch block and ST-segment elevation in leads V1–3. The clinical phenotype may be unmasked by administration of ajmaline or procainamide. The only effective treatment is with an implantable cardiac defibrillator.

Cardiac manifestations: SCD, syncope, arrhythmia.

C–F

Carney syndrome

Association of atrial myxomas, myxomas in other sites (e.g. breast/skin), spotty pigmentation, and endocrine overactivity (e.g. pituitary or testicular tumours). AuD inheritance; mutation is in the *PRKAR1A* gene (chromosome 17). Manifests in third decade of life. ↑ bilateral myxomas/develop recurrence than sporadic cases.

Cardiac manifestations: cardiac myxoma.

Also known as: familial myxoma, Carney complex.

di George syndrome

A disorder resulting from deletion of the *TBX1* gene on chromosome 22; leads to parathyroid and thymic hypoplasia (hypocalcaemia and low T cell counts), and cardiac outflow tract defects. Individuals typically have micrognathia, low-set ears, a short philtrum, and a small mouth.

Cardiac manifestations: tetralogy of Fallot, truncus arteriosus, interrupted aortic arch, right-sided aortic arch, aberrant right subclavian artery.

Also known as: 22q11.2 deletion syndrome, Shprintzen syndrome, velocardiofacial syndrome.

Dressler syndrome

Myocardial infarction (MI)-associated pericarditis, usually occurs after 2–3 weeks. May occur after several months. An autoimmune aetiology is suspected due to delay in development, presence of anti-heart antibodies, altered lymphocyte subsets, complement activation, frequent recurrence, associated pleural effusions, and response to steroids.

Cardiac manifestations: pericarditis.

Also known as: post-MI syndrome.

Duchenne muscular dystrophy

An X-linked disorder of the dystrophin gene. There is severe skeletal muscle weakness and cardiomyopathy. Fibrosis primarily affects the posterolateral and posterobasal left ventricular (LV) wall.

Cardiac manifestations: dilated cardiomyopathy, heart failure, heart block, syncope, arrhythmia (supraventricular > ventricular).

Ebstein's anomaly

A malformation where the TV leaflets are abnormally attached, with downward displacement of the TV. The proximal RV lies between the atrioventricular (AV) ring and the origin of the valve, and is 'atrialized'. A small RV chamber exists. TV tissue is dysplastic.

Cardiac manifestations: tricuspid regurgitation, arrhythmia, pulmonary stenosis/atresia, VSD, ostium primum atrial septal defect (ASD), and accessory pathways (50% of patients).

Eisenmenger syndrome

Any systemic-to-pulmonary circulation shunt, eventually leading to reversed or bidirectional flow, with pulmonary hypertension and cyanosis. First described in a 32-year-old man with a VSD in 1897.

Cardiac manifestations: heart failure, arrhythmia.

Ellis–Van Creveld syndrome

An AuR condition characterized by short stature (metaphyseal dysplasia), polydactyly, and dysplastic nails/teeth; 50% of sufferers have cardiac features, most commonly, primum ASD.

Cardiac manifestations: ASD, coarctation of the aorta, hypoplastic left heart, patent ductus arteriosus (PDA).

Also known as: chondroectodermal dysplasia.

Emery–Dreifuss muscular dystrophy

A triad of muscular contractures (elbow, ankle, and posterior cervical), progressive skeletal myopathy, and cardiac manifestations. SCD at age <50 years is common. Generally, an X-linked recessive trait (*EMD* gene); AuD inheritance is also seen. *EMD* encodes a protein (emerin) important for skeletal/cardiac muscle function.

Cardiac manifestations: sinus bradycardia, atrial fibrillation/flutter, heart block, ventricular tachycardia/fibrillation, heart failure.

Fabry disease

A rare, X-linked recessive lysosomal storage disorder involving a deficiency of the enzyme α-galactosidase. There is a resulting accumulation of globotriaosylceramide throughout the body. Systemic features include renal impairment, angiokeratomas, neuropathy, and corneal keratopathy. Enzyme replacement therapy is available.

Cardiac manifestations: ventricular hypertrophy, heart failure.

Also known as: Anderson–Fabry disease.

Fallot's tetralogy

A congenital cardiac condition causing cyanosis in the newborn; 10% of all cases of congenital heart disease. Slightly more common in ♂. Risk factors include maternal alcohol use, diabetes, and rubella infection in pregnancy. In Fallot's tetralogy, there is an intact ventricular septum, and in Fallot's pentalogy, there is also an ASD or patent foramen ovale.

Cardiac manifestations: pulmonary stenosis, VSD, overriding aorta, RV hypertrophy.

Also known as: tetralogy of Fallot.

Friedreich's ataxia

A spinocerebellar degenerative disease characterized by limb and trunk ataxia, skeletal deformities, dysarthria, loss of tendon reflexes, muscular weakness, and cardiomyopathy. The condition is inherited in an AuD manner, due to an amplified, unstable GAA trinucleotide repeat found in the *FXN* gene on chromosome 9.

Cardiac manifestations: heart failure, LV hypertrophy, septal hypertrophy, dilated cardiomyopathy, atrial arrhythmias.

Friedreich's sign

Sudden collapse of the cervical veins in diastole, occurring in constrictive pericarditis.

Also known as: mediastinopericarditis adhesiva.

H–L

Heyde's syndrome

Association of gastrointestinal bleeding with calcific aortic stenosis; bleeding is due to acquired von Willebrand's disease type 2a, caused by high aortic valve shear stress. This leads to haemorrhage from gut arteriovenous malformations. Bleeding ceases after valve replacement.

Cardiac manifestations: aortic stenosis.

Holt–Oram syndrome

An AuD condition where upper limb dysplasia is associated with a secundum ASD. Limb dysplasia may be subtle (e.g. distally placed/triphalangeal thumbs) or severe (e.g. hypoplastic clavicles and phocomelia).

Cardiac manifestations: ASD, VSD, mitral valve prolapse, PDA.

Also known as: heart–hand syndrome.

Hurler syndrome

An AuR mucopolysaccharide storage disorder due to α-L-iduronase deficiency (lysosomal enzyme). Manifests as coarse facial features, corneal clouding, hepatosplenomegaly, learning difficulties, and cardiac problems. Most sufferers die in the first decade.

Cardiac manifestations: restrictive cardiomyopathy, coronary artery stenosis, and valvular thickening and regurgitation.

Also known as: mucopolysaccharidosis type IH.

Jervell and Lange–Nielsen syndrome

An AuR condition associated with deafness caused by mutations in the *KVLQT1* or *KCNE1* gene. Both encode parts of the delayed rectifier potassium ion channel and result in QT interval prolongation.

Cardiac manifestations: ventricular arrhythmias, SCD.

Also known as: long QT syndrome 5.

Kartagener's syndrome

Triad of situs inversus, abnormal sinuses, and immotile cilia. Patients have recurrent respiratory infections, sinusitis, bronchiectasis, and infertility. Some have ↓ immunoglobulin A. AuR inheritance.

Cardiac manifestations: situs inversus.

Also known as: Siewert's syndrome, primary ciliary dyskinesia.

Kawasaki disease

Acute vasculitis that affects children, which manifests with fever, cervical lymphadenopathy, bilateral conjunctivitis, and erythema or desquamation of the palms and soles. The aetiology is unknown.

Cardiac manifestations: coronary artery aneurysms, MI, SCD.

Also known as: mucocutaneous lymph node syndrome.

Kearns–Sayre syndrome

A triad of AV block, pigmentary retinopathy, and progressive external ophthalmoplegia. It is caused by deletion of several mitochondrial genes. In most cases, it occurs sporadically and is not inheritable.

Cardiac manifestations: heart block, syncope.

Also known as: chronic progressive external ophthalmoplegia with ragged red fibres.

Leber hereditary optic neuropathy

A mitochondrial encephalomyopathy characterized by painless loss of vision in young men. Associated with ↓ PR interval and pre-excitation.

Cardiac manifestations: arrhythmia.

Also known as: Leber's optic atrophy.

Lenegre–Lev disease

An AuD disorder mapped to chromosome 19, defined by wide QRS complexes that progress to complete heart block. Distinct from progressive familial heart block type II, which has narrow QRS complexes.

Cardiac manifestations: heart block, syncope.

Also known as: progressive familial heart block type I, Lev's disease.

Libman–Sacks syndrome

A late cardiac manifestation of systemic lupus erythematosus. Found in 50% of patients with fatal lupus. Sterile vegetations on valve leaflets/chordae, consisting of fibrin, neutrophils, lymphocytes, and histiocytes. Mitral/aortic valves most commonly affected, often clinically silent; regurgitation more common than stenosis. Similar lesions occur in antiphospholipid syndrome. Women more commonly affected.

Cardiac manifestations: non-infectious endocarditis.

Also known as: verrucous endocarditis.

Løffler's endocarditis

Rare manifestation of eosinophilic myocarditis. The aetiology may be helminthic infection or leukaemia, but it is often idiopathic. The lungs are often involved (Løffler's syndrome). Acute eosinophilic myocarditis involves vasculitis and cardiac ischaemia. Chronically, myocardial fibrosis leads to restrictive cardiomyopathy.

Cardiac manifestations: acute coronary syndrome, restrictive cardiomyopathy.

Also known as: eosinophilic myocarditis.

Lown–Ganong–Levine syndrome

Ventricular pre-excitation characterized by short PR interval, normal QRS duration, and paroxysms of supraventricular tachycardia. Those without tachycardia may be described as having accelerated AV nodal conduction. Intranodal or paranodal fibres bypassing the AV node have been found in some, but most electrophysiology studies have found other reasons for tachycardias (e.g. dual-nodal physiology).

Cardiac manifestations: arrhythmia.

Also known as: atrial tachyarrhythmia with short PR interval.

Lutembacher's syndrome

The combination of mitral stenosis (congenital or acquired) and ASD (congenital or iatrogenic), with left-to-right shunt.

Cardiac manifestations: RV overload (large ASD), pulmonary oedema (small ASD), atrial fibrillation.

M–T

Marfan syndrome

A disorder resulting from mutations in the *FBN1* gene on chromosome 15 encoding fibrillin 1, which constitutes the microfibrils that make up the extracellular matrix. Features include tall stature, kyphosis, scoliosis, pectus excavatum, upward lens dislocation, retinal detachment, and cardiac abnormalities; 75% are AuD; the rest occur sporadically.

Cardiac manifestations: mitral valve prolapse and regurgitation, dilated sinuses of Valsalva, aortic root dilatation with aortic regurgitation and ↑ risk of dissection, and arrhythmias.

Morquio's syndrome

A mucopolysaccharide storage disorder, inherited in an AuR manner. Two types are recognized. Type A is caused by deficiency of galactosamine-6-sulfatase. Type B is caused by deficiency in β-galactosidase. Clinical features include short stature, skeletal and joint abnormalities, cloudy corneas, hepatomegaly, and cardiac involvement.

Cardiac manifestations: aortic and mitral regurgitation, heart failure (results from infiltrative cardiomyopahthy or valvular regurgitation).

Also known as: mucopolysaccharidosis IVB (MPSIVB).

Noonan syndrome

A dysmorphic syndrome characterized by cardiac anomalies, short stature, low-set ears, hypertelorism, deafness, and bleeding diathesis. AuD inheritance. Has sometimes been called 'male Turner syndrome', but affects both sexes and has no chromosomal abnormalities.

Cardiac manifestations: pulmonary stenosis, ASD, VSD, hypertrophic cardiomyopathy.

Ortner's syndrome

First described as compression of the recurrent laryngeal nerve by a dilated left atrium in mitral stenosis, leading to vocal cord paresis and a hoarse voice. Now used with any non-malignant cardiac/intrathoracic process that damages the recurrent laryngeal nerve. The left nerve is more affected than the right, due to its longer course around the aortic arch.

Pompe disease

An AuR metabolic disorder caused by accumulation of glycogen within lysosomes due to deficiency of the enzyme α-glucosidase. The disease can present in infants, juveniles, or adults. Treatment is available in the form of enzyme replacement therapy.

Cardiac manifestations: LV hypertrophy, outflow tract obstruction, heart failure.

Also known as: glycogen storage disease type II, acid maltase deficiency.

Prinzmetal's angina

Angina resulting from spasm of a coronary artery. It may be prevented by long-acting calcium channel antagonists.

Cardiac manifestations: MI, heart block, syncope.

Also known as: variant angina.

Romano–Ward syndrome

The most common form of long QT syndrome. Unlike other forms of long QT syndrome, Romano–Ward syndrome only affects the electrical properties of the heart. An AuD condition caused by mutation in genes on chromosomes 3, 4, 7, 11, and 21 encoding different components of both sodium and potassium ion channels.

Cardiac manifestations: prolonged QT interval, SCD.

Also known as: long QT syndrome.

Stokes–Adams syndrome

Syncope caused by cardiac arrhythmia. Initially referring to syncope secondary to heart block, it is now more generally applied to any arrhythmic cause of collapse.

Cardiac manifestations: syncope, arrhythmia, heart block.

Also known as: Spens syndrome, Morgagni disease.

Taussig–Bing syndrome

A congenital anomaly in which the aorta arises from the RV, the pulmonary artery arises from both ventricles, and there is an associated VSD.

Tietze syndrome

Inflammation of the costochondral cartilages of unknown aetiology. There is characteristic swelling of the cartilages, which distinguishes the syndrome from other types of costochondritis, and the swelling may persist after the pain has resolved. Mostly men in their third decade are affected.

Cardiac manifestations: chest pain.

Timothy syndrome

An AuD inherited condition characterized by syndactyly, autism spectrum disorders, and facial dysmorphogenesis. Results from mutations in the *CACNA1C* gene, which encodes a calcium channel subunit.

Cardiac manifestations: prolonged QT interval, SCD.

Also known as: long QT syndrome 8.

Townes–Brocks syndrome

An AuD condition describing the association of an imperforate anus with abnormalities of the kidneys, hand, foot, and ear; sporadically associated with cardiac malformations.

Cardiac manifestations: VSD, ASD.

Turner syndrome

A disorder resulting from the absence of one of the X chromosomes (XO). Features include short stature, absence of secondary sexual characteristics, webbing of the neck, cubitus valgus, and lymphoedema. It is one of the most common chromosomal abnormalities.

Cardiac manifestations: coarctation of the aorta.

W

Wenkebach's phenomenon

A form of second-degree AV heart block characterized by progressive lengthening of the PR interval on the ECG until a P wave is not conducted to the ventricles.

Williams syndrome

A congenital condition characterized by elfin facial features, hypercalcaemia, outgoing personality, learning difficulties, strabismus, and dental anomalies. Varied cardiac abnormalities are recognized. AuD transmission is observed if this syndrome is inherited and is due to deletion of 7q11.23.

Cardiac manifestations: supravalvular aortic stenosis, peripheral pulmonary artery stenosis, LV hypertrophy, sinus of Valsalva dilatation, coronary artery dilatation, SCD.

Also known as: Williams–Beuren syndrome.

Wolff–Parkinson–White syndrome

Tachyarrhythmias that occur as a result of an accessory AV pathway, typified by ECG features in sinus rhythm of a PR interval <120ms and a QRS duration >120ms caused by a delta wave, representing antegrade conduction through the accessory pathway. Patients can have intermittent conduction via this pathway, leading to variable ECG patterns.

Cardiac manifestations: arrhythmia.

Also known as: auriculoventricular accessory pathway syndrome.

Chapter 17

Drugs for the heart

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Note on the organization of this chapter

- This chapter aims to provide an overview of medications commonly prescribed in cardiology.
- Drugs have been grouped based on their primary mechanism of action or primary indication where possible.
- The contents of this chapter are not a substitute for a dedicated pharmacology resource, which should be consulted, if in doubt, before prescribing any medication.

Antianginal agents: nitrates

Examples in this class

- *Short-acting:* GTN.
- *Long-acting:* ISMN, ISDN.

Pharmacology

Mode of action

- These drugs act as nitric oxide (NO) donors.
- Nitrates have powerful vasodilatory and venodilatory effects to improve coronary blood flow while ↓ preload and afterload.
- Myocardial workload is ↓, resulting in ↓ in oxygen demand.
- Nitrates protect against exercise-induced ischaemia by preventing coronary spasm and coronary vasoconstriction induced by exercise.

Metabolism

- *Liver:* GTN—prodrug, rapidly metabolized to produce NO.
- *Excretion:* predominantly renal.
- *Half-life:* GTN—3min, ISMN—5h.

Indications and place in therapy

- *Short-acting nitrates:* S/L GTN is used for acute symptomatic relief of angina or prophylactically to prevent the development of predictable exertional chest pain.
- *Long-acting nitrates*: should be considered as adjunctive therapy in prophylaxis against anginal chest pain in those already on a β-blocker and/or non-DHP CCB.

Contraindications and cautions

- *Contraindications:* nitrate hypersensitivity, AS, hypotensive and hypovolaemic conditions, hypertrophic constrictive myopathy, cardiac tamponade, constrictive pericarditis, MS, marked anaemia, head trauma, cerebral haemorrhage. Concurrent sildenafil (Viagra®) therapy.
- *Cautions:* hypothyroidism, closed-angle glaucoma.

Usual dosing

- With long-acting nitrates, to prevent tolerance, dosing should be asymmetric to allow for a nitrate-free period (4–12h/day). An interval should be left between doses where a bd regimen is prescribed (i.e. 8 a.m. and 2 p.m.—nitrate levels will then ↓ overnight).
- Slow-release (SR) formulations release nitrate slowly over 15–20h, allowing for a nitrate-free period within each 24h. These should not be prescribed bd for prophylaxis against angina.

See Table 17.1 for usual doses.

Monitoring

- Little specific monitoring is required for patients taking nitrates, other than ensuring BP is maintained, with SBP of >100mmHg.
- The patient should be advised on managing nitrate-induced headaches and counselled carefully on asymmetric dosing/the importance of a nitrate-free period if appropriate.

Table 17.1 Doses for nitrates

Agent	Dose
Glyceryl trinitrate	Tablets/spray: one tablet/spray (400–800mcg) under the tongue, repeat every 5–10min. If chest pain does not resolve within 20min, urgent medical advice should be sought
	Infusion: 0.5–10mg/h titrated to control chest pain. Maintain systolic BP above 100mmHg
Isosorbide mononitrate	Short-acting: 20–60mg bd is commonly prescribed but may be subtherapeutic
	Long-acting formulations: 30–120mg daily
Isosorbide dinitrate	Short-acting: 20–60mg bd

Adverse effects (selected)

- *Hypotension:* patients should be advised to sit down before taking S/L nitrates. Significant hypotension and syncope can occasionally result.
- *Headache:* occurs due to cerebral vasodilatation. Can be reduced by spitting out the S/L tablet after resolution of chest pain (sprays cannot be dealt with in this way). Simple analgesics (preferably paracetamol-based) may be used.

Selected interactions

- *Anticoagulants:* infusion of GTN reduces the anticoagulant effect of heparins.
- *Sildenafil, tadalafil, vardenafil:* hypotensive effects of nitrates are significantly enhanced; avoid concomitant use.

Clinical evidence

- Nitrates have been shown to reduce the frequency and severity of angina attacks if taken chronically at appropriate doses.
- A meta-analysis of trials examining the effect of nitrates demonstrated improved exercise duration and protection against effort-induced angina.[1]

Reference

1. Wei J, Wu T, Yang Q, *et al*. Nitrates for stable angina: a systematic review and meta-analysis of randomized clinical trials. *Int J Cardiol*. 2011;**146**(1):4–12.

Antianginal agents: potassium channel activators

Examples in this class

- Nicorandil.

Pharmacology

Mode of action

- Nicorandil is a K^+ channel activator with a nitrate-like action.
- Opening of the K^+ channel leads to arterial vasodilatation and reduced afterload, whereas the nitrate effect leads to venous dilatation and reduced preload.

Metabolism

- *Liver:* undergoes extensive hepatic metabolism to inactive metabolites.
- *Excretion:* predominantly renal.
- *Half-life:* 1h.

Indications and place in therapy

- Nicorandil is indicated as a second-line therapy for chronic coronary syndrome (stable angina) to reduce symptom frequency and improve exercise tolerance where β-blockers, CCBs, and nitrates have been tried or are contraindicated.

Contraindications and cautions

- *Contraindications:* cardiogenic shock, LVF with low filling pressures and hypotension, hypersensitivity to nicorandil, pregnancy, and breastfeeding.
- *Cautions:* depleted blood volume, low SBP, acute pulmonary oedema, or acute MI with acute LVF and low filling pressures.
- Patients should be advised not to drive or operate machinery until it is established that their performance is not impaired.

Usual dosing

- A dose of 5–10mg bd is recommended initially.
- The dose should be ↑ gradually, according to clinical response, to a maximum dose of 40mg bd (10–20mg bd is the usual chronic dose).

Monitoring

- BP should be monitored at intervals during therapy.
- The drug dose should be adjusted to optimize symptomatic relief of angina episodes.

Adverse effects (selected)

- *Headache:* occurs commonly, especially in the early phase of treatment; consider a lower starting dose.
- *Dizziness and hypotension:* especially at higher doses.

- *Peripheral vasodilatation leading to flushing:* occurs commonly.
- *Ulceration:* GI ulceration, skin ulceration, and ulcers of the mucosal membranes have been reported. These tend to be refractory to treatment and most only respond to withdrawal of nicorandil treatment.
- *Angio-oedema:* occurs uncommonly.

Selected interactions

- *Antihypertensives:* enhanced hypotensive effect with the addition of nicorandil.
- *PO corticosteroids:* ↑ in gastric erosions when used in combination with nicorandil; avoid concomitant use.
- *PDE-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil):* due to risk of severe hypotension, concomitant use of nicorandil and PDE-5 inhibitors is contraindicated.

Clinical evidence

The Impact of Nicorandil in Angina (IONA, 2002) trial evaluated nicorandil against standard antianginal treatment in those with chronic stable angina. The nicorandil arm reported a modest reduction in the composite primary end point of coronary heart disease death, non-fatal MI, or unplanned hospital admission for cardiac chest pain (15.5% placebo vs 13.1% nicorandil; $P = 0.014$).

Antianginal agents: ranolazine

Pharmacology

Mode of action

- The mode of action of ranolazine is not well understood, despite the agent being in use for a number of years.
- Ranolazine inhibits late Na^+ channels in the heart.
- Reduced accumulation of Na^+ leads to ↓ intracellular Ca^{2+} load, facilitating myocardial relaxation and ↓ diastolic stiffness.
- Ranolazine reduces the abnormalities of ventricular repolarization and contractility seen during episodes of ischaemia, with a resultant improvement in myocardial function and perfusion.
- The antianginal effects of ranolazine are independent of changes in BP and HR.

Metabolism

- *Liver:* metabolized by the CYP3A pathway, but effect of metabolites not well established.
- *Excretion:* predominantly renal.
- *Half-life:* 7h.

Indications and place in therapy

- Indicated as a second-line therapy for chronic coronary syndrome (stable angina) to ↓ symptom frequency and ↑ exercise tolerance where β-blockers, CCBs, and nitrates have been tried or are contraindicated.
- Ranolazine may be particularly useful in patients with hypotension/bradycardia, as it has minimal effects on these parameters.

Contraindications and cautions

- *Contraindications:* severe renal (creatinine clearance (CrCl) <30mL/min) or ≥ moderate hepatic impairment (see Box 17.1), pregnancy, and breastfeeding.
- *Cautions:* initiate and titrate doses carefully in those with mild to moderate renal impairment (CrCl 30–80mL/min), mild hepatic dysfunction, and moderate to severe HF (NYHA classes III–IV), elderly patients, and those with low body weight (<60kg) and QT prolongation.

Usual dosing

- SR tablets 375mg bd initially, increasing after 2–4 weeks to 500mg SR bd and, if necessary, to a maximum of 750mg SR bd.

Monitoring

- *BP/pulse:* at baseline and within 4 weeks of initiation or dose change; usually minimal effects on BP/HR.
- *ECG monitoring:* may be considered after initiation to ensure no significant QTc prolongation.

Adverse effects (selected)

- *GI:* diarrhoea, constipation, nausea, and vomiting are common. Anorexia, ↓ appetite, and dehydration are uncommon.
- *Syncope, postural dizziness, headache:* may require dose reduction.
- *Skin:* allergic dermatitis, urticaria, rash, pruritus, hyperhidrosis.

Box 17.1 Hepatic impairment

There is no universally accepted mechanism for determining hepatic impairment for drug elimination. However, the European Medicines Agency[*] suggests use of the Child–Pugh classification:[**]

Degree of impairment	Child–Pugh Score
No significant impairment	≤4
Mild	5–6
Moderate	7–9
Severe	≥10

[*] Committee for Medicinal Products for Human Use. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. 2005.

[**] Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG (ed.) (1964). *The Liver and Portal Hypertension*. Philadelphia, PA: Saunders, pp. 50–64.

- *Central nervous system (CNS):* somnolence, tremor, fatigue. Rarely, disorientation, amnesia, depressed level or loss of consciousness.
- *Eye and ear:* blurred vision, visual disturbance, vertigo, tinnitus.

Selected interactions

In general, concomitant use with other QT-prolonging agents should be avoided. Use with agents that ↓ K^+ may predispose to QT prolongation. Some specific interactions include:

- *Antiarrhythmics:* avoid concomitant disopyramide/amiodarone.
- *Antibacterials*: clarithromycin and telithromycin possibly ↑ ranolazine levels; avoid concomitant use. Rifampicin reduces ranolazine levels; avoid concomitant use.
- *Antifungals*: ketoconazole, itraconazole, posaconazole, and voriconazole ↑ plasma levels of ranolazine; avoid concomitant use.
- *Antivirals*: possible ↑ in ranolazine levels; check individual agents for details.
- *β-blockers*: avoid concomitant use with sotalol.
- *Grapefruit juice*: may ↑ ranolazine levels; avoid concomitant consumption.

Clinical evidence

- Three placebo-controlled studies have confirmed the efficacy of ranolazine alone or as an adjunct to standard antianginal therapies (atenolol, amlodipine, and diltiazem) to improve symptomatic control in chronic stable angina (MARISA, 2004; CARISA, 2004; ERICA, 2006).
- MERLIN-TIMI-36 investigated the use of ranolazine compared with placebo in the treatment of non-ST-segment elevation ACS, but failed to show an impact on the primary end point of occurrence of CV death, MI, or recurrent ischaemia.

Antiarrhythmic agents: class Ic

Examples of this class

- Flecainide, propafenone.

Pharmacology

Mode of action

- Blocks Na^+ channels, slowing conduction velocity and prolonging the refractory period of the AVN.
- Leads to QRS prolongation, with minimal effect on the action potential duration.

Metabolism

- *Liver:* propafenone primarily undergoes hepatic metabolism.
- *Excretion:* flecainide is primarily renally excreted.
- *Half-life:* flecainide—20h; propafenone—depends on individual (range 2–10h).

Indications and place in therapy

Focal atrial tachycardia

- *Acute treatment:* in haemodynamically stable patients, IV class Ic agents are a third-line option (after adenosine, followed by β-blockers or non-DHP CCBs).
- *Chronic treatment:* PO class Ic agents should be considered in those requiring chronic therapy, but for whom ablation is not desired or feasible.

Atrioventricular re-entrant tachycardia

- *Acute treatment:* consider class Ic agents in antidromic AVRT if vagal manoeuvre and adenosine fail.
- *Chronic treatment:* can be considered in those requiring chronic therapy, but for whom ablation is not desired or feasible.

Pre-excited atrial fibrillation

- *Acute treatment:* IV class Ic agents may be considered in those who are haemodynamically stable.

Atrial fibrillation

- *Acute treatment:* first-line therapy for pharmacological cardioversion of new-onset AF in those without haemodynamic instability.
- *Chronic treatment:* first-line therapy in patients for whom a rhythm control strategy is used and there are no signs of structural heart disease.

Atrial flutter

- Class Ic agents should not be used in this setting. These agents may slow the flutter circuit sufficiently to allow 1:1 conduction through the AVN, paradoxically resulting in ↑ HR and haemodynamic instability.

Contraindications and cautions

- *Contraindications*: ↓ LVEF, cardiac conduction defects, significant valvular disease, previous MI or other IHD, long-standing AF.
- *Cautions*: post-operative AF, older patients.

Usual dosing

- *Flecainide*: 50mg bd, can ↑ to 150mg bd. If using IV, then 2mg/kg to a maximum of 150mg.
- *Propafenone*: 150mg tds, can ↑ to 300mg bd.

Adverse effects (selected)

- *Common*: arrhythmias, dizziness, fever, anxiety.
- *EP changes:* changes in pacing threshold, AV block, and cardiac arrest are recognized complications.

Selected interactions

In general, concomitant use with other QT-prolonging agents should be avoided. Use with agents that ↓ K^+ may predispose to QT prolongation. Some specific interactions include:

- *Amiodarone:* ↑ concentration of flecainide and propafenone, reduce dose of flecainide/propafenone.
- β-*blockers:* ↑ risk of CV side effects, including bradycardia (also applies to other rate-limiting medications).
- *Digoxin:* concentration ↑ by propafenone, adjust dose.
- *Diuretics:* ↑ risk of hypokalaemia, which may ↑ risk of TdP.
- *Haloperidol:* ↑ QT interval, avoid combining with flecainide.
- *Ivabradine:* ↑ risk of TdP, avoid.
- *Macrolide antibiotics:* ↑ QT interval, avoid combining with flecainide.
- *Sildenafil:* ↑ QT interval, avoid combining with flecainide.

Clinical evidence

- Flecainide has been studied in a number of small trials, which showed significantly higher rate of cardioversion for AF vs placebo, amiodarone, and sotalol.
- Evidence against use in AFl comes from one study demonstrating lack of efficacy of flecainide,[1] and a putative ↑ risk of 1:1 conduction through the AVN with class Ic agents.

Reference

1. Crijns HJ, Van Gelder IC, Kingma JH, *et al*. Atrial flutter can be terminated by a class III antiarrhythmic drug but not by a class IC drug. *Eur Heart J*. 1994;**15**:1403–8.

Antiarrhythmic agents: class III

Examples in this class

- Amiodarone, dronedarone.

Pharmacology

Mode of action

- Class III antiarrhythmics; principally act by blocking cardiac K^+ channels, leading to prolonged action potential/repolarization times.
- No effect on conduction velocity, combined with prolonged action potential and repolarization times, prevents circuit arrhythmias.

Metabolism

- *Liver:* amiodarone extensively metabolized and can affect metabolism of many other drugs, has less impact on other medications.
- *Excretion:* primarily via liver and bile.
- *Half-life:* amiodarone average of 58 days; dronedarone 13–19h.

Indications and place in therapy

Atrial fibrillation

Acute treatment

- Amiodarone is first line for pharmacological cardioversion in those with IHD/structural heart disease or CCF with ↓ LVEF.

Chronic treatment

- *Dronedarone:* recommended in those with normal LV function and without pathological LVH.
- *Amiodarone:* recommended in those with HF.

Other amiodarone indications

- *Wide QRS tachycardia:* third line after vagal manoeuvres ± adenosine.
- *Focal AT:* can consider (IV) as third line after adenosine and β-blockers or non-DHP CCBs. Can be considered for chronic therapy if ablation and/or β-blockers or non-DHP CCBs fail.
- *AFl:* can consider (IV) if haemodynamically stable after β-blockers/non-DHP CCBs, IV ibutilide/dofetilide, and synchronized cardioversion have been tried or considered.
- *AVRT:* consider in refractory antidromic AVRT.

Contraindications and cautions

General contraindications

- Severe conduction disturbances, including sinus node dysfunction and second- or third-degree heart block.

Amiodarone

- *Contraindications:* avoid IV bolus in CCF, iodine sensitivity, and thyroid dysfunction.
- *Cautions:* acute porphyria, elderly, CCF, hypokalaemia, bradycardia.

Dronedarone

- *Contraindications:* bundle branch block, amiodarone-associated liver/lung toxicity, permanent AF, long QT interval.
- *Cautions:* CAD, hypokalaemia, hypomagnesaemia.

Usual dosing

(See Table 17.2)

Monitoring

Acute administration

- BP and ECG monitoring during, and for ≥15min after, infusion.

Amiodarone

- *TFTs and LFTs:* before treatment and every 6 months.
- *K^+:* required before treatment.
- *CXR:* required before treatment.

Dronadarone

- *HF:* regular clinical monitoring signs/symptoms.
- *ECG:* before treatment and then every 6 months.
- *Renal function*: before treatment and 7 days after initiation.
- *LFTs:* at baseline, at 1 week, then monthly for 6 months, then 3-monthly for the first year, then periodically.

Adverse effects (selected)

All agents

- Arrhythmias, cardiac conduction disorders, QT prolongation, hypersensitivity, hypotension.

Amiodarone

- *Corneal micro-deposits:* reverses if treatment stopped. Must stop to prevent blindness if vision impairment or optic neuritis/neuropathy.
- *Hepatotoxicity:* treatment should be discontinued if signs of liver disease develop or severe deterioration in liver function detected.
- *Photosensitivity reaction:* warn and advise to keep out of the sun.
- *Pulmonary toxicity:* lung fibrosis can occur and should be considered in those developing progressive dyspnoea or cough.
- *Thyroid dysfunction:* contains iodine, can result in hyper-/hypothyroidism.

Dronedarone

- *HF:* stop if new-onset/worsening CCF or ↓ LVEF occurs.
- *Hepatotoxicity:* life-threatening liver failure can occur. Should be discontinued if consecutive ALT measurements >3 times the upper limit of normal (ULN).
- *Pulmonary toxicity:* as per amiodarone.

Table 17.2 Doses for amiodarone and dronedarone

Drug	Acute cardioversion	Chronic therapy
Amiodarone	5–7mg/kg given IV over 1–2h	600mg in divided doses for 1 week, then 400mg in divided doses for 1 week, then 200mg od. Given PO
Dronedarone	N/A	400mg bd

Selected interactions

Amiodarone has a large number of potential interactions. A careful drug history should be taken, and potential interactions confirmed prior to prescription.

- *Aminophylline**: may ↓ K+ and ↑ risk of TdP.
- *Antiarrhythmics:* may ↑ concentration of class Ic agents, avoid co-administration.
- β*-blockers**: may worsen CV side effects, avoid co-administration.
- *CCBs (non-DHP)**: amiodarone ↑ cardiodepressive effects, avoid co-administration.
- *Digoxin**: may ↑ digoxin concentration, requires careful monitoring.
- *Loop diuretics**: may ↓ K+ and ↑ risk of TdP.
- *Macrolide antibiotics**: both ↑ QT interval, avoid co-administration.
- *DOACs:* co-administration with dabigatran or edoxaban ↑ anticoagulant effect. Dabigatran dose should be reduced.
- *Selective serotonin reuptake inhibitors (SSRIs)**: both ↑ QT interval, avoid co-administration.
- *Statins**: predicted ↑ risk of rhabdomyolysis, adjust statin dose.
- *Thiazide diuretics**: may ↓ K+ and ↑ risk of TdP.
- *Ticagrelor*: may ↑ ticagrelor concentration, use with caution.
- *Vitamin K antagonists:* amiodarone ↑ anticoagulant effect.

(* Interactions occur with dronedarone and amiodarone.)

Clinical evidence

Dronedarone

- The EURIDIS and ADONIS trials both showed that dronedarone (cf. placebo) ↑ the median time to AF recurrence.
- The ATHENA trial demonstrated patients with AF given dronedarone (cf. placebo) had ↓ rate of primary end point (composite of hospitalization due to CV events or death) of 31.9% vs 39.4.
- The PALLAS trial randomized those with permanent AF to either dronedarone or placebo. This showed dronedarone ↑ rates of HF, stroke, and CV death in those with permanent AF.
- The ANDROMEDA trial examined the effects of usual care vs usual care and dronedarone in patients with new-onset HF; this trial was stopped early due to ↑ risk of death in the dronedarone group.

Amiodarone

- As an older medication, amiodarone has been subjected to fewer trials. It has been shown to be superior to quinidine and sotalol in maintaining SR in those with AF after cardioversion.
- Amiodarone has also been shown to have a higher rate of cardioversion to SR in acute AF, compared with digoxin or verapamil (both of which have minimal efficacy in cardioverting AF). Amiodarone has also been shown to have similar cardioversion rates to those of quinidine and class Ic agents.

Anticoagulants: direct thrombin inhibitors

Examples in this class

- Dabigatran.

Pharmacology

Mode of action

- Dabigatran binds reversibly to thrombin.
- This prevents coagulation activation.

Metabolism

- *Liver:* dabigatran is metabolized to a number of active metabolites.
- *Excretion:* primarily renal (85%).
- *Half-life:* 12–17h.

Indications and place in therapy

- *Stroke prophylaxis in AF:* in those requiring anticoagulation for AF, dabigatran is a first-line option (other first-line options are factor Xa inhibitors).
- *VTE treatment:* a first-line option (other first-line options are factor Xa inhibitors).
- *Non-cardiac indications:* dabigatran can be considered for VTE prophylaxis after knee/hip replacement surgery.

Contraindications and cautions

- *Contraindications:* active bleeding, APS, prosthetic heart valves, neoplastic disease, oesophageal varices/peptic ulcers, recent neuro-/spine/ophthalmic surgery, intracranial haemorrhage, significant bleeding risk.
- *Cautions:* indwelling epidural catheter, IE, bleeding disorders, weight <50kg, gastritis/gastro-oesophageal reflux disease (GORD), recent biopsy/major trauma, low platelet count.

Usual dosing

Stroke prophylaxis in atrial fibrillation

- *Standard dosing:* in those ≤74 years—150mg bd; in those ≥80 years—110mg bd (in those aged 75–79 years, either dose can be considered).
- *Dose reduction:* consider ↓ dose of 110mg bd in those on verapamil, at ↑ risk of bleeding, or with moderate renal impairment.

Venous thromboembolism treatment

- *Standard dose:* 150mg bd after ≥5 days of parenteral anticoagulation (e.g. with LWMH), in those ≥80 years—110mg bd (in those aged 75–79 years, either dose can be considered).
- *Dose reduction:* consider ↓ dose of 110mg bd in those at ↑ risk of bleeding or with moderate renal impairment.

Monitoring

- *Bleeding*: if bleeding is present, dabigatran should be stopped (see ➔ Anticoagulants: reversibility, pp. 762–3).
- *Renal function:* at baseline and monitor annually in renal impairment and the elderly.
- Routine anticoagulation monitoring is not required.

Adverse effects (selected)

- Anaemia, bleeding, GI disturbance, hepatic dysfunction/hyperbilirubinaemia.

Selected interactions

The majority of interactions with dabigatran relate to ↑ drug concentration/exposure and resulting bleeding risk. These drugs include:

- Amiodarone
- Aspirin/cyclo-oxygenase (COX) inhibitors
- Azole antifungal agents
- Dronedarone
- P2Y12 inhibitors
- Ranolazine
- SSRIs
- Verapamil.

Other interactions

- *Phenytoin:* reduced exposure to dabigatran.
- *Antiviral agents:* variable effects on dabigatran.

Clinical evidence

Dabigatran was compared with warfarin in the RE-LY trial (2009). A dose of 150mg bd ↓ stroke/systemic embolism by 35% and did not have an effect on major bleeding events. The 110mg bd dose was non-inferior to warfarin in terms of stroke risk and had 20% fewer bleeding events.

Anticoagulants: factor Xa inhibitors

Examples in this class

- Apixaban, edoxaban, rivaroxaban.

Pharmacology

Mode of action

- These agents selectively inhibit factor Xa. Factor Xa is responsible for catalysing the conversion of prothrombin to thrombin.
- By blocking factor Xa, these agents block the coagulation cascade.

Metabolism

(See Table 17.3)

Indications and place in therapy

- *Stroke prophylaxis in AF:* in those requiring anticoagulation for AF, dabigatran is a first-line option; another first-line option is a direct thrombin inhibitor (e.g. dabigatran).
- *VTE treatment:* a first-line option (another first-line option is dabigatran).
- *Non-cardiac indications:* apixaban and rivaroxaban can be considered for VTE prophylaxis after knee/hip replacement surgery.

Contraindications and cautions

- *Contraindications:* active bleeding, APS, prosthetic heart valves, neoplastic disease at high risk of bleeding, oesophageal varices/peptic ulcers, recent neuro-/spine/ophthalmic surgery, intracranial haemorrhage, significant bleeding risk.
- *Cautions*: indwelling epidural catheter, bronchiectasis, older individuals, IE, bleeding disorders, gastritis/GORD, recent biopsy/major trauma, low platelet count.
- *Low weight*: there is ↑ bleeding risk in those with low weight.

Usual dosing

Atrial fibrillation stroke prophylaxis

- *Apixaban:* 5mg bd.
- *Edoxaban:* 60mg od.
- *Rivaroxaban:* 20mg od.
- ↓ doses should be considered in some individuals (see Table 17.4).

Table 17.3 Pharmacokinetics of factor Xa inhibitors

	Apixaban	Edoxaban	Rivaroxaban
Half-life (h)	9–14	10–14	5–9
Excretion (%)	Bile 75 Renal 25	Faecal 60 Renal 35	Hepatic 65 Renal 35
Metabolism	25% via CYP3A4 pathway	30% via CYP3A4 pathway	65% via CYP3A4/5 pathway

Table 17.4 Indications for reduced dosing in factor Xa inhibitors

	Apixaban*	Edoxaban	Rivaroxaban
Criteria	Age >80 years Weight <61kg Creatinine ≥133 micromol/L	Weight <61kg	CrCl 30–49mL/min
Reduced dose	2.5mg bd	30mg od	15mg od

* Reduced dose of apixaban should be used if ≥2 criteria are present.

Venous thromboembolism treatment

- *Apixaban:* 10mg bd for 7 days, then 5mg bd.
- *Edoxaban:* 60mg od, with ≥5 days of parenteral anticoagulation.
- *Rivaroxaban:* 15mg bd for 21 days, then 20mg od.

Monitoring

- *Renal function:* monitor at baseline and periodically as indicated.
- *Hepatic function:* edoxaban only, at baseline, and periodically if treated for >1 year.
- Routine anticoagulation monitoring is required.

Adverse effects (selected)

- Anaemia, bleeding, GI upset, headache, hypersensitivity, skin reactions.
- See ➔ Anticoagulants: reversibility, pp. 762–3 for reversal of DOAC effects.

Selected interactions

The majority of factor Xa inhibitor interactions ↑ drug concentration/exposure and/or result in ↑ bleeding risk. These drugs include:

- Aspirin/COX inhibitors, azole antifungals, dronedarone, macrolide antibiotics, prostaglandins, P2Y12 inhibitors, and SSRIs.

Other drug interactions

- *Carbamazepine:* moderately ↓ exposure and may ↑ risk of thrombus.

Clinical evidence

- *Apixaban:* the ARISTOTLE trial (2011) compared apixaban with warfarin in AF. Apixaban 5mg bd ↓ stroke/systemic embolism by 21%, ↓ major bleeding by 31%, and ↓ death by 11%.
- *Edoxaban:* the ENGAGE AF-TIMI 48 trial (2013) compared apixaban with warfarin in AF. Edoxaban 60mg daily led to a similar rate of stroke/systemic embolism and death, with a 20% ↓ in major bleeding.
- *Rivaroxaban:* the ROCKET-AF study (2011) compared rivaroxaban with warfarin in AF. Rivaroxaban 20mg daily showed a similar risk of stroke/systemic embolism, major bleeding, and death.

Anticoagulant: fondaparinux

Pharmacology

Mode of action

- Fondaparinux is a synthetic pentasaccharide which binds to antithrombin. This leads to ↑ inhibition of factor Xa.

Metabolism

- *Liver:* nil of note.
- *Excretion:* renally excreted unchanged.
- *Half-life:* 17–21h.

Indications and place in therapy

- *ACS:* fondaparinux is used as anticoagulation in NSTEMI or UA.
- *VTE prophylaxis:* after major orthopaedic or abdominal surgery, or in medical patients immobilized due to acute illness.

Contraindications and cautions

- *Contraindications:* bleeding, IE.
- *Cautions:* peptic ulcer disease, bleeding disorders, elderly patients, low weight, recent ophthalmic or spinal surgery, epidural/spinal anaesthesia.

Usual dosing

- 2.5mg od (given s/c) for up to 8 days or until angioplasty.

Monitoring

- None generally required.

Adverse effects (selected)

- Anaemia, chest pain, dyspnoea, GI upset, haemorrhage, liver dysfunction, platelet dysfunction.

Selected interactions

Interactions generally relate to ↑ bleeding risk. Specific interactions include:

- Aspirin/COX inhibitors
- Other NSAIDs
- SSRIs
- P2Y12 inhibitors
- Prostaglandins.

Clinical evidence

- In OASIS-5 (2006), fondaparinux was compared with enoxaparin in ACS and was found to be non-inferior for a composite outcome of MI, death, or refractory ischaemia. However, it was shown to have a 48% lower bleeding risk.

Anticoagulants: vitamin K antagonists

Examples in this class

- Warfarin.

Pharmacology

Mode of action

- VKAs block the vitamin K epoxide reductase enzyme.
- Blocking this enzyme reduces the amount of active vitamin K.
- Synthesis of clotting factors II, VII, IX, and X is vitamin K-dependent; without vitamin K, their production is lowered.
- Also prevents synthesis of the anticoagulant factors proteins C and S, which have shorter half-lives (thus, VKAs have a procoagulant effect in the first few days of use).

Metabolism

- *Liver:* extensively metabolized via a variety of pathways; as a result, warfarin is very susceptible to the effects of other medications.
- *Excretion:* predominantly renal.
- *Half-life:* 20–60h.

Indications and place in therapy

Stroke prevention in atrial fibrillation

- *General therapy:* VKAs are considered second-line therapy for stroke prevention after direct thrombin inhibitors/factor Xa inhibitors.
- *MS/mechanical heart valves:* in patients with AF and these underlying conditions, VKAs should be used as the first-line agent.

Venous thromboembolism

- VKAs are considered second-line therapy for VTE treatment after direct thrombin inhibitors/factor Xa inhibitors.

Prosthetic heart valves

- VKAs are the first-line anticoagulant of choice in prosthetic heart valves.

Contraindications and cautions

- *Contraindications:* <48h post-partum, haemorrhagic stroke, significant bleeding.
- *Cautions:* GI bleed or peptic ulcer disease, IE, ↑ bleeding risk, <7 days post-partum, recent stroke, recent surgery, thyroid dysfunction, uncontrolled hypertension.

Usual dosing

Initiation

- A number of different induction regimen have been proposed. Table 17.5 provides selected examples for illustrative purposes.
- In general, for AF stroke prophylaxis, lower-dose initiation regimens are recommended to ↓ the risk of over-anticoagulation, and thus the risk of major bleeding. Higher-dose anticoagulation strategies may be required in those being treated for VTE or with prosthetic heart valves.
- Warfarin initiation should be tailored to the individual patient, and local guidance should be followed where available.

Table 17.5 Initiation dosing for warfarin

Protocol	INR	Fennerty *et al.*[*]	Gedge *et al.*[**]	Janes *et al.*[†]
Day 1	<1.4	10	10	3[‡]
Day 2	<1.8	10	5	3[‡]
	1.8–2.0	1	1	
	>2.0	0	0	
Day 3	<2.0	10	5	3[‡]
	2.0–2.2	5	4	
	2.3–2.5	4	4	
	2.6–2.9	3	3	
	3.0–3.2	2	2	
	3.3–3.5	1	1	
	>3.5	0	0	

[‡] The Janes *et al.*'s protocol suggests giving a standard dose of 3mg/day for the first 8 days and then checking the INR.

[*] Fennerty *et al*. Flexible induction dose regimen for warfarin and prediction of maintenance dose. *BMJ*. 1984;**288**:1268–70;

[**] Gedge *et al*. A comparison of a low-dose warfarin induction regimen with the modified Fennerty regimen in elderly inpatients. *Age Ageing*. 2000;**29**:31–4;

[†] Janes *et al*. Safe introduction of warfarin for thrombotic prophylaxis in atrial fibrillation requiring only a weekly INR. *Clin Lab Haem*. 2004;**26**:43–7.

- Additional anticoagulation with heparin/LMWH should be used for the first 5 days, or until the INR is within the target range for VTE and prosthetic heart valve patients.

Maintenance therapy

- Maintenance dosing depends on the patient and the target INR.
- In general, if the INR is below target, the maintenance dose should be ↑. If the INR is above target, the dose should be ↓ (or omitted if the INR is very high).

Monitoring

International normalized ratio

- Regular monitoring of the INR is required in those on warfarin. The target levels depend on the underlying condition.
- The exact timing of measurements depends on length of therapy and stability of previous results.
- A time in therapeutic range (TTR) should be calculated as a measure of anticoagulation efficacy (see Box 17.2).
- A high TTR (≥70%) should be aimed for; if below this level, switching to an alternate class of anticoagulation should be considered.
- Patients at greater risk of low TTR can be calculated by using the SAMe-TT2R2 score.

Box 17.2 Calculating time in therapeutic range

Several methods are available for calculating the time in therapeutic range (TTR). The most commonly used is the Rosendaal method[*]:

- It calculates the percentage of days in range
- By taking an example of a patient with an INR initially at 2.5 and then at 1.5, the TTR can be calculated:

Step	Method	Example
1	Take the two test dates of interest and work out the number of days apart	1 January to 12 January—11 days
2	Determine the target INR range	2.0–3.0
3	Assume the patient's INR changed in a linear fashion between the two dates	Started at 2.5 and reached 1.5 by losing 0.1 INR/day
4	Determine the number of days the INR was in target range	Day 1 (2.5) Day 6 (2.0) Hence 6 days
5	Determine the percentage of days in range	6/11 days TTR: 55%

- Calculators are available to provide values over multiple readings.

[*] Rosendaal *et al*. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;**69**(3):236–9.

Adverse effects (selected)

- Bleeding, alopecia, GI upset.
- See ➔ Anticoagulants: reversibility, pp. 762–3 for reversal of VKA effects.

Selected interactions

Food

- The effect of VKAs can be significantly reduced by foods containing vitamin K. Vitamin K is found in green tea and some green vegetbles (e.g. spinach).
- Cranberrys, pomegranates, and grapefruit all reduce warfarin metabolism and may ↑ the INR.
- Alcohol can also significantly impact the effect of VKAs.
- In general, patients should be advised to keep their diet consistent (i.e. no large variations in the amount of vitamin K-containing foods, alcohol, etc.), rather than complete abstention.

Drugs

VKAs are subject to a large number of potential interactions, and a full drug history should be taken from patients and potential interactions checked prior to initiating warfarin or any new medication. Some particularly important interactions are listed below and should prompt close monitoring of the INR:

- *Amiodarone:* ↑ anticoagulant effect.

- *Antibiotics:* including penicillin, cephalosporin, fluoroquinolone, and macrolide classes. Variable effect on INR.
- *Antifungals:* azole class of antifungal agents can ↑ the anticoagulant effect of warfarin; regular monitoring of INR and dose adjustments advised.
- *Antiplatelet agents:* ↑ bleeding risk; combined therapy should only be considered under expert guidance.
- *COX inhibitors/NSAIDs:* ↑ bleeding risk.
- *SSRIs:* ↑ risk of bleeding when co-administered.

Clinical evidence

- *Compared with placebo:* warfarin has been compared against placebo or aspirin in a large number of small trials in patients with AF. When summarized in a meta-analysis,[1] warfarin reduced the risk of stroke by ~60% ,compared with placebo.
- *Compared with DOACs:* warfarin was used as the comparator arm for all recent trials of direct thrombin inhibitors and factor Xa inhibitors (see ➲ Clinical evidence, p. 753; ➲ Clinical evidence, p. 755).

Reference

1. Hart RG, Pierce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have non-valvular atrial fibrillation. *Ann Intern Med*. 2007;**146**:857–67.

Anticoagulants: reversibility

- All anticoagulants, by their nature, ↑ the risk of bleeding (see Table 17.6).
- If bleeding occurs, anticoagulation reversal should be considered.

Warfarin

- Warfarin ↓ the amount of active vitamin K available for synthesis of vitamin K-dependent clotting factors (factors II, VII, IX, and X).
- Reversed by providing vitamin K (generally slow) or by replacing clotting factors directly (generally faster) (see Table 17.7).
- Reversal method depends on the degree of bleeding (see Table 17.8).

Non-vitamin K antagonist oral anticoagulants

- Directly inhibit clotting factors and do not affect their synthesis.
- Unlike VKAs, reversal is achieved by inactivating the DOAC itself.

Table 17.6 Definition of the extent of bleeding

Bleeding	Definition	Examples
Major bleeding	Life- or limb-threatening that requires complete reversal in <8h*	Intracranial haemorrhage Upper gastrointestinal bleeding
Non-major bleeding	Bleeding that is not life- or limb-threatening	Nosebleeds Superficial bleeding

* See Keeling D, *et al*. Guidelines on oral anticoagulation with warfarin, fourth edition. *Br J Haematol*. 2011;**154**(3):311–24.

Table 17.7 Vitamin K reversal

Reversal speed	Approach	Details
Rapid (complete, 10–15min)	IV prothrombin complex concentrate (PCC) and IV vitamin K	PCC contains factors II, VII, IX, and X; administration directly replaces depleted clotting factors, providing complete reversal
Fast (partial)	IV fresh frozen plasma (FFP) and IV vitamin K	FFP contains vitamin K-dependent factors but only partially corrects coagulopathy
Prompt (6–8h)	IV vitamin K	↑ endogenous manufacture of clotting factors
Slow (24h)	PO vitamin K	↑ endogenous manufacture of clotting factors, but slower absorption
Very slow (days)	Hold warfarin	Vitamin K epoxide reductase inhibition slowly ↓, allowing clotting factor production

Source: data from Keeling D, *et al*. Guidelines on oral anticoagulation with warfarin, fourth edition. *Br J Haematol*. 2011;**154**(3):311–24; Hanley JP, *et al*. Warfarin reversal. *J Clin Pathol*. 2004;**57**(11):1132–9.

Table 17.8 Summary recommendations for warfarin reversal

Clinical situation	Recommended approach
Major bleeding	Stop warfarin IV PCC (25–50 units/kg) IV vitamin K (5mg)
Major bleeding (if PCC not available)	Stop warfarin IV FFP IV vitamin K (5mg)
Non-major bleeding	Stop warfarin IV vitamin K (1–3mg)
INR >8.0, but no bleeding	Hold warfarin for 1–2 doses Reduce maintenance dose PO vitamin K 1–5mg
INR 5.0–8.0, no bleeding	Hold warfarin for 1–2 doses Reduce maintenance dose

PCC, prothrombin complex concentrate; FFP, fresh frozen plasma.

Source: data from Keeling D, *et al*. Guidelines on oral anticoagulation with warfarin, fourth edition. *Br J Haematol*. 2011;**154**(3):311–24.

Dabigatran

- Idarucizumab is a monoclonal antibody which rapidly reverses the anticoagulant effects of dabigatran.
- Indicated in major bleeding or when emergency reversal is required.

Factor Xa inhibitors

- Andexanet alfa is a recombinant form of factor Xa which binds to apixaban or rivaroxaban.
- Indicated for reversal of apixaban or rivaroxaban in uncontrolled or life-threatening bleeding.

Heparins

- Heparins anticoagulate by binding to, and activating, antithrombin III.
- The effect of UFH can be complete reversed with protamine sulfate. Protamine sulfate will partially reverse LMWH.

Fondaparinux

- Does not have an effective antidote at present.

Ciraparantag

- An anticoagulant antidote that is effective against factor Xa inhibitors, direct thrombin inhibitors, and heparins.
- Binds directly to anticoagulants, inhibiting their effects.

Anticoagulants: switching agents

- In some individuals, it will be necessary to switch anticoagulation regimens.
- This requires a balance of bleeding and thrombotic risks, and should be done carefully.

Switching from warfarin

- Warfarin and other VKAs have variable pharmacokinetic profiles.
- An INR level should be taken, and warfarin stopped.
- When the new agent is started depends on the INR result (see Table 17.9).

Table 17.9 Recommendations for switch from warfarin to another anticoagulant

INR	Recommendation
<2.0	New agent can be initiated immediately
2.0–2.5	New agent can be initiated the next day
>2.5	Recheck INR in 1–3 days

Adapted from Steffel *et al*. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J*. 2018;**39**:1330–93.

Switching from a non-vitamin K antagonist oral anticoagulant

- DOACs have a clear and predictable pharmacokinetic profile.
- *Switching to LMWH:* this can be started when the next dose of the DOAC is due.
- *Switching to another DOAC:* can be started when the next dose of the original DOAC is due.
- *Switching to a VKA:* given the wide individual variation in onset of action of VKAs, the DOAC and VKA should be co-administered until the INR is within the normal range. DOACs can affect INR measurements, and this should be measured immediately before DOAC doses. If switching from edoxaban, a half-dose of this agent should be used.

Antiplatelet agents: overview

Antiplatelet agents are used to reduce the risk of arterial thrombus formation by preventing platelet activation and aggregation. Antiplatelet agents have a role in primary and secondary prevention of CVD.

Platelet aggregation

Platelet aggregation occurs as a result of formation of fibrinogen bonds between GPIIb/IIIa receptors expressed on the surface of activated platelets. Platelets are activated by a number of pathways, with specific inhibitors (see Table. 17.10).

Table 17.10 Platelet activation pathways and drug inhibitors

Pathway	Drug inhibitors
Thromboxane A2	Aspirin
ADP-mediated	Clopidogrel
	Prasugrel
	Ticlopidine
	Ticagrelor
Thrombin	Heparin (weak)
	Bivalirudin
Glycoprotein IIb/IIIa receptors	Abciximab
	Eptifibatide
	Tirofiban

ADP, adenosine diphosphate.

Antiplatelet agents: aspirin

Pharmacology

Mode of action

- Blocks the thromboxane A_2 pathway of platelet activation by irreversibly acetylating COX.
- The effect of aspirin persists for the lifespan of the platelet.

Metabolism

- *Liver:* CYP2C19 ± CYP3A.
- *Excretion:* 80–100% in urine.
- *Half-life:* 2–3h for 75mg od dose (longer for higher doses).

Indications and place in therapy

- Important benefit in secondary prevention for all presentations of CVD, including ACS, chronic stable angina, after CABG, ischaemic stroke, and peripheral vascular disease (PVD).
- Aspirin is no longer recommended for routine use for primary prevention, as the benefit-to-risk ratio is finely balanced.
- Often prescribed after implantation of intracardiac occluder devices or TAVI to prevent thrombus formation during epithelialization (≤6 months).

Contraindications and cautions

- *Contraindications:* known allergy, active peptic ulceration, history of recent GI bleeding, history of recent intracranial bleeding, bleeding disorders (e.g. haemophilia), and severe liver disease.
- *Cautions:* asthma, uncontrolled hypertension, previous peptic ulcers (prophylactic proton pump inhibitor (PPI) or H2 receptor antagonists may be considered).

Usual dosing

- *ACS:* 300mg once only, then 75mg od.
- *TIA/ischaemic stroke:* 300mg once only, then 75mg od.

Monitoring

- Not routinely recommended (see Box 17.3).

Box 17.3 Aspirin resistance

- Aspirin effectiveness is affected by ‘aspirin resistance’.
- This occurs relatively commonly in up to 10% of treated patients.
- Rarely identified, as platelet activity testing is not widely used.

Adverse effects (selected)

- Aspirin, even at low doses, can precipitate bronchospasm in up to 20% of asthmatic adults.
- Gastric side effects are common and range from nausea to major GI bleeds. Aspirin is associated with a higher risk of bleeding from duodenal ulcers than from gastric ulcers, and occurs more commonly in the early days of treatment. Risk of bleeding should be assessed (see Box 17.4).

Box 17.4 Risk factors for gastrointestinal bleeding with aspirin

- *Age:* risk doubles with each decade of life above age of 55 years
- *Men:* risk is twice as high in men as in women
- *Gastrointestinal:* ulcer, bleed, perforation, *Helicobacter pylori* infection
- *Concomitant medications:* such as NSAIDs, anticoagulants, selective serotonin reuptake inhibitors
- *Serious comorbidities:* such as cardiovascular disease, liver or kidney disease, diabetes
- *Prolonged NSAID use:* such as for osteoarthritis, rheumatoid arthritis, and chronic low back pain
- *Social history:* excess alcohol or heavy smoking

Selected interactions

- *Analgesics:* avoid concomitant use with NSAIDs, as this ↑ the risk of adverse effects.
- *Anticoagulants:* ↑ risk of bleeding with warfarin and other anticoagulants. Avoid concomitant use unless there is a compelling indication for both.
- *Antidepressants:* ↑ risk of bleeding with SSRIs and venlafaxine.
- *Cytotoxics:* aspirin ↓ excretion of methotrexate; avoid concomitant use where possible, or ensure close monitoring of methotrexate dose.

Clinical evidence

- *Secondary prevention:* data to support the use of aspirin in secondary prevention of CVD have been accruing since the 1980s. The Second International Study of Infarct Survival (ISIS-2) trial showed use of aspirin 300mg in acute MI reduced mortality by 23%. The Antithrombotic Trialists' Collaboration concluded that post-AMI, aspirin reduced the risk of further CV events by 25% (number needed to treat (NNT) = 28 over 2 years).
- *Primary prevention:* the role of aspirin in primary prevention is less clear, as the CV benefits must be balanced against the risk of adverse events, in particular, the risk of GI bleeds. A meta-analysis suggested that aspirin ↓ the risk of CV events from 0.57%/year to 0.51%/year, but ↑ significant bleeds by 0.03%/year. This is supplemented by the ARRIVE trial, which showed no benefit in CV outcomes, with ↑ risk of bleeding. Aspirin should not be prescribed for primary prevention of CVD (ESC Class III recommendation).

Antiplatelet agents: clopidogrel

Pharmacology

Mode of action

- Thienopyridines irreversibly block the binding of ADP to platelet receptors, and hence prevent the expression of the active GPIIb/IIIa receptor.
- Ticlopidine, the first agent in this class, has been superseded in clinical practice by the use of clopidogrel, which has fewer serious adverse effects. Prasugrel was launched in 2009, and 2010 saw the introduction of ticagrelor.
- Clopidogrel is a prodrug, converted through CYP2C19 to its active metabolite.

Metabolism

- *Liver*: CYP2C19 conversion into active metabolite.
- *Excretion:* 50% urine, 50% biliary.
- *Half-life:* clopidogrel, 6h. Active metabolite, 30min. However, affects platelet function for 7–10 days.

Indications and place in therapy

- Monotherapy used for secondary prevention in patients post-MI/stroke or with PVD (when intolerant of aspirin).
- Used in combination with aspirin for patients following ACS (STEMI and NSTEMI) and as an adjunct to aspirin to prevent stent thrombosis.
- Should not be used for primary prevention of CV events.
- May be used for prevention of CV events following procedures such as intracoronary stent implantation or PFO closure, or following TAVI.

Contraindications and cautions

- *Contraindications:* hypersensitivity to clopidogrel, severe hepatic impairment, active pathological bleeding.
- *Cautions:* patients at ↑ risk of bleeding, recent CVA, renal impairment.

Usual dosing

- *Post-PCI to prevent stent thrombosis (with aspirin):* 300mg once only, and then 75mg od.
- *ACS (with aspirin):* 300mg once only, then 75mg od.
- *Secondary prevention of CVD:* 75mg od.

Monitoring

- None routinely (see Box 17.5).

Box 17.5 Clopidogrel resistance

- Similarly to aspirin, 'resistance' can affect the clinical effect of clopidogrel.
- Occurs in about 10% of treated patients.
- Unclear mechanism of underlying resistance.

Adverse effects (selected)

- The single most troubling adverse effect of clopidogrel is skin rash. Should be distinguished from self-limiting X-ray contrast media-induced skin rash, which occurs early (within 1 week of PCI), to avoid unnecessary cessation of clopidogrel. Minor rashes may be managed by use of antihistamines, but often alternative therapies, such as prasugrel or ticagrelor, will be required.
- GI side effects are reported relatively commonly and include diarrhoea, abdominal pain, and dyspepsia.
- Bleeding and bruising are common, particularly where aspirin and clopidogrel are used in combination. Small risk of haematological disorders, including thrombocytopenia and neutropenia.

Selected interactions

- *PPIs:* omeprazole has been shown to ↓ antiplatelet activity of clopidogrel and should not be used concomitantly.
- *Opioids:* co-administration delays clopidogrel absorption.
- *NSAIDs:* ↑ risk of GI bleeding.
- *CYP2C19 inhibitors:* (e.g. fluoxetine) will reduce conversion of clopidogrel into its active metabolite.
- *Other antiplatelet/anticoagulants:* ↑ risk of bleeding.

Clinical evidence

- In the CAPRIE (Clopidogrel versus Aspirin in Patients at risk of Ischemic Events) study (1997), clopidogrel demonstrated a small advantage over aspirin in terms of protecting patients from recurrent CV events. As the clinical advantage over aspirin for this indication is small and the relative cost is large, clopidogrel should only be employed for monotherapy in patients who are unable to tolerate aspirin as first line. There is no evidence to support the use of clopidogrel for primary prevention of CVD.
- The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study (2000) compared aspirin monotherapy with clopidogrel and aspirin dual therapy in patients for up to 9 months post-NSTEMI and demonstrated a 2% reduction in major CV events with DAPT. The COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) study (2005) demonstrated that aspirin/clopidogrel dual therapy reduced death and CV events at 4 weeks following the acute event, compared with aspirin alone.

Antiplatelet agents: prasugrel

Pharmacology

Mode of action

- Thienopyridine class drug which blocks the ADP receptor on platelets; the same mode of action as that of clopidogrel and ticagrelor.

Metabolism

- *Liver:* prasugrel is a prodrug, which is metabolized in the liver to its active metabolite.
- *Excretion:* two-thirds urinary, one-quarter fecal.
- *Half-life:* ~7h (active metabolite).

Indications and place in therapy

- Prasugrel, used in combination with aspirin, is licensed for prevention of atherothrombotic events in patients with ACS (STEMI, NSTEMI, or UA) undergoing primary or delayed PCI.
- Prasugrel is more effective than clopidogrel in patients with diabetes.

Contraindications and cautions

- *Contraindications:* hypersensitivity, history of CVA or TIA, active bleeding disorder, severe hepatic impairment.
- *Cautions:* those at ↑ risk of bleeding—age over 75 years and body weight <60kg, renal and moderate hepatic impairment, Asian patients (due to limited clinical experience), pregnancy, and lactation.

Usual dosing

- *ACS undergoing PCI:* 60mg once only, then 10mg od (maintenance dose should be reduced to 5mg daily if used in patients over the age of 75 years or those of low body weight of <60kg).

Monitoring

- None routinely undertaken.

Adverse effects (selected)

- Bleeding occurs commonly and is particularly problematic in the elderly (>75 years) or patients of low body weight (<60kg)—a lower maintenance dose may be considered in these groups.
- Anaemia, epistaxis, GI haemorrhage, and haematuria are all commonly reported.
- Rashes.

Selected interactions

- *Anticoagulants:* concomitant use of prasugrel with warfarin is not routinely recommended due to ↑ risk of bleeding. If an anticoagulant and an antiplatelet agent are both required, clopidogrel should ideally be used.
- *Niacin:* ↑ risk of bleeding.
- Unlike clopidogrel, no effect of PPIs on drug action has been demonstrated.

Clinical evidence

- The TRITON TIMI 38 (Trial to Access Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction) study compared prasugrel with clopidogrel (on a background of aspirin therapy) in patients with ACS undergoing immediate or delayed PCI, and demonstrated significantly fewer major CV events in the prasugrel-treated group, but at the expense of ↑ risk of bleeding.
- ISAR-REACT 5 compared prasugrel with ticagrelor (both in addition to aspirin) in patients with ACS undergoing invasive evaluation. There was a reduction in the composite of death, repeat MI, and stroke with the prasugrel group, and no difference in bleeding risk.

Antiplatelet agents: ticagrelor

Pharmacology

Mode of action

- Thienopyridine class drug which blocks the ADP receptor on platelets; the same mode of action as that of clopidogrel and prasugrel.

Metabolism

- *Liver:* ticagrelor is a prodrug, which is converted into its active metabolite in the liver.
- *Excretion:* biliary.
- *Half-life:* 7h for ticagrelor, 8.5h for active metabolite.

Indications and place in therapy

- Indicated (in combination with aspirin) to prevent atherothrombotic events in those with ACS for up to 12 months.
- Used to prevent acute stent thrombosis (in combination with aspirin) in those with ACS who have undergone PCI.
- Can be used for longer-term DAPT after MI (up to 3 years).

Contraindications and cautions

- *Contraindications:* history of intracranial bleeding, acute bleeding.
- *Cautions:* chronic lung disease (asthma/COPD), bradycardia, second/third-degree AV block, sick sinus syndrome, previous hyperuricaemia, ↑ risk of bleeding.

Usual dosing

- *After ACS and to prevent stent thrombosis:* 180mg once only, followed by 90mg bd.
- *Extended treatment 12 months after ACS:* 60mg bd.

Monitoring

- *Renal function:* should be checked 1 month after initiation.

Adverse effects (selected)

- Bradycardia, breathlessness, GI disturbance, gout, bleeding, headache, rash.

Selected interactions

- *Amiodarone:* ↑ effect of ticagrelor, ↑ bleeding risk.
- *Anticoagulants:* concomitant use of ticagrelor with warfarin is not routinely recommended due to ↑ risk of bleeding. If an anticoagulant and an antiplatelet agent are both required, clopidogrel should ideally be used.
- *Antifungals:* azole antifungals ↑ the effect of ticagrelor and should be avoided.
- *Antivirals:* generally ↑ the effect of ticagrelor and associated bleeding risk. Co-administration should generally be avoided.

- *Macrolides:* azithromycin and clarithromycin both ↑ the effect of ticagrelor and associated bleeding risks.
- *Phenytoin:* ↓ the effect of ticagrelor; co-administration should be avoided.
- *Rifampicin:* ↓ the effect of ticagrelor; co-administration should be avoided.

Clinical evidence

- The PLATO trial examined patients with ACS and compared ticagrelor with clopidogrel. This showed that those given ticagrelor had a lower risk of the composite end point of CVD, MI, or stroke. There was no significant difference in major bleeding events.
- ISAR-REACT 5 compared prasugrel with ticagrelor (both in addition to aspirin) in patients with ACS undergoing invasive evaluation. There was a reduction in the composite of death, repeat MI, and stroke with the prasugrel group, and no difference in bleeding risk.
- PEGASUS TIMI 54 examined the role of continuing DAPT (aspirin and ticagrelor) for >12 months in those who had had a heart attack 1–3 years previously. Use of a 60mg bd dose showed a reduction in the composite end point of CVD, MI, and stroke. There was no difference in intracranial heamorrhage or fatal bleeding.

Antiplatelet agents: glycoprotein IIb/IIIa inhibitors

Examples in this class

- Abciximab, eptifibatide, tirofiban.

Pharmacology

Mode of action

- The GPIIb/IIIa receptor is found on platelets and is required for fibrinogen binding.
- *Abciximab:* a monoclonal antibody which inhibits the GPIIb/IIa receptor.

Metabolism

- *Liver:* abciximab likely to be opsonized by the reticuloendothelial system; there is minimal metabolism of eptifibatide or tirofiban.
- *Excretion:* all are predominantly renal.
- *Half-life:* abciximab 10–30min; eptifibatide 2.5h; tirofiban 2h.

Indications and place in therapy

- *STEMI/NSTE ACS:* GPIIb/IIIa inhibitors should be considered as a bailout strategy in situations where there is evidence of no-reflow or a thrombotic complication.

Contraindications and cautions

- *Contraindications:* abnormal bleeding or ↑ INR, haemorrhagic stroke, previous intracranial disease, stroke in last 30 days, thrombocytopenia.
- *Cautions:* acute pericarditis, aortic dissection, cardiogenic shock, peptic ulcer disease or GI bleeding, haematuria, ↑ risk of bleeding, major surgery in last 3 months, severe HF, CPR in the last 2 weeks, uncontrolled hypertension, vasculitis.

Usual dosing

Initiation of GPIIb/IIIa agents should be under specialist advice only. General dosing instructions are as follows:

- *Abciximab:* 250mcg/kg over 10–60min (IV), followed by 125ng/kg/min (maximum 10mcg/min) for 12h.
- *Eptifibatide:* 180mcg/kg (IV), followed by 2mcg/kg/min for ≤72h.
- *Tirofiban:* 25mcg/kg given over 3min (IV), then an infusion of 150ng/kg/min for 12–24h (maximum duration 48h).

Monitoring

- *At baseline:* coagulation, FBC, and renal function.
- *FBC:* measure within 6h of starting treatment and then at least daily.

Adverse effects (selected)

- *Abciximab:* bleeding, chest pain, GI disturbance, hypotension, visual changes.
- *Eptifibatide:* bleeding, headache, thrombocytopenia.
- *Tirofiban:* arrhythmia, AV block, bleeding, CCF, shock, thrombocytopenia.

Selected interactions

- *Anticoagulants:* ↑ risk of bleeding.
- *Antiplatelet agents:* ↑ risk of bleeding.

Clinical evidence

- Six large-scale trials have examined the effect of GPIIb/IIIa inhibitors on clinical outcomes in those with non-ST-segment elevation ACS with various comparisons: PRISM (tirofiban, 1998), PRISM-PLUS (tirofiban, 1998), PARAGON-A, (lamifiban, 1998), PARAGON-B (lamifiban, 2002), PURSUIT (eptifibatide, 1998), and GUSTO-IV ACS (abciximab, 2001). A meta-analysis of the results has demonstrated a 9% relative reduction in death or MI (1% absolute reduction), with a similar absolute ↑ in major bleeding.[1]
- There is limited evidence of the use of GPIIb/IIIa inhibitors in patients with STEMI. However, pre-hospital use has been shown to ↑ bleeding without benefit (FINESSE, 2008 and TIME 2, 2010).
- Of note, these trials were performed before widespread use of P2Y12 inhibitors; as such, the risk–benefit in patients treated with these agents is unclear.

Reference

1. Boersma E, Harrington RA, Moliterno DJ, *et al*. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomized clinical trials. *Lancet*. 2002;**359**:189–98.

β-adrenoceptor blockers (β-blockers)

Examples in this class

- *Non-selective:* carvedilol, labetalol, nadolol, propranolol.
- *β1-selective:* atenolol, bisoprolol, metoprolol, nebivolol.

Pharmacology

Mode of action

- β-blockers block the action of noradrenaline at β-adrenoceptors (located in the myocardium, the circulatory system, and elsewhere), inhibiting sympathetic stimulation of HR and myocardial contractility.
- β-blockers slow the firing of pacemaker cells in the SAN and also ↓ AVN conduction.
- They have anti-ischaemic and antiarrhythmic effects.
- β-blockers ↓ BP, although the exact mechanism is unclear. May be due to ↓ circulating renin levels or ↓ sympathetic tone.

Pharmacology

(See Table 17.11 for details.)

Table 17.11 Characteristics of commonly prescribed β-blockers

Agent	Half-life (h)	Excretion/metabolism	Lipid solubility	Cardioselectivity
Atenolol	6–7	Renal	–	+
Bisoprolol	10–12	Renal and liver	+	++
Carvedilol	7–10	Faecal	+	–
Metoprolol	3–7	Renal and liver	+	+
Nebivolol	10+	Renal and faecal	+++	+++

Choice of agent

This should take into account the indication, clinical trial data, and properties of individual β-blockers.

Key properties include:

- Duration of action—longer-acting agents are preferred
- Water or lipid solubility, which will influence adverse effects
- Cardioselectivity.

Indications and place in therapy

- *HF*: all patients with symptomatic HF and LV systolic dysfunction, initiated as early as possible following diagnosis in stable patients—*only bisoprolol, carvedilol, and nebivolol are licensed in the UK*.
- *Post-MI secondary prevention:* all patients following an MI, initiated during the inpatient phase of treatment.
- *Angina*: first line for all patients—aim for resting HR of 50–60bpm.
- *AF*: first line when using a rate control strategy.

Contraindications and cautions

- *Contraindications:* asthma or bronchospasm (NB β-blockers may be considered in HF under specialist supervision), second- or third-degree heart block, severe PVD, those on verapamil.
- *Cautions:* COPD (if evidence of reversibility), uncontrolled CCF, sick sinus syndrome, those on diltiazem, hypotension or bradycardia, PVD.

Usual dosing

- Optimal β-blockade is often described as control of resting HR to between 50 and 60bpm.
- Usual starting and target doses of β-blockers are listed in Table 17.12.
- Consider ↓ starting doses if borderline bradycardia, HF, or hypotension, if on antihypertensive therapy, or in older patients.
- For optimal cardioprotective effects, ↑ maximum tolerated dose.

Table 17.12 Doses for commonly used β-blockers

Agent	Starting	dose	Target dose
Atenolol	25–50mg	daily	50–100mg daily
Bisoprolol	2.5mg	daily	10mg daily
In HF	1.25mg	daily	↑ over 10–12 weeks, aim for 10mg daily
Carvedilol	12.5mg	daily	50mg daily
In HF	3.125mg	bd	↑ over 10–12 weeks, maximum dose weight-dependent
Metoprolol	25mg	bd	50–100mg tds

Monitoring

- Obtain baseline BP and pulse before initiation and after dose changes.
- If no adverse effects, review within 4 weeks and consider dose ↑.
- Lethargy and/or impotence are not necessarily indications for drug withdrawal. Side effects are frequently distressing but may wear off over time. Address patient concerns, but they should be strongly encouraged to persevere with therapy in view of the cardiac benefits.
- If medication discontinuation proves necessary, withdraw the β-blocker slowly to avoid reflex tachycardia.

Adverse effects (selected)

- *Bradycardia* (HR <50bpm): consider dose ↓, exclude heart block.
- *Symptomatic hypotension:* consider dose ↓, exclude heart block.
- *Bronchospasm:* review the need for β-blocker and consider alternative drug class. If compelling indication, use a cardioselective β-blocker, with extreme caution and under specialist supervision.
- *Fatigue:* may dissipate during therapy.
- *Cold extremities:* use gloves/socks in cold weather.
- *Sleep disturbances:* consider a water-soluble agent.

Selected interactions

- *α-blockers:* enhanced hypotensive effect.
- *AADs:*
  - Amiodarone—↑ risk of myocardial depression, AV block, and bradycardia
  - Flecainide—↑ risk of myocardial depression and bradycardia
  - Lidocaine—↑ risk of toxicity with propranolol
  - Propafenone—↑ plasma concentration of metoprolol and propranolol.
- *Antidepressants*:
  - Citalopram, escitalopram, paroxetine—↑ metoprolol plasma concentration
  - ↑ hypotensive effect with monoamine oxidase inhibitors.
- *Antimalarials:* mefloquine—↑ risk of bradycardia.
- *CCBs:* ↑ hypotensive effect. Diltiazem—risk of AV block, bradycardia. Verapamil—severe hypotension and HF.
- *Ciclosporin:* ↑ plasma concentration with carvedilol.
- *Clonidine:* ↑ risk of withdrawal hypertension.
- *Diuretics*: enhanced hypotensive effect.
- *Sympathomimetics* (e.g. adrenaline, dobutamine): ↑ risk of severe hypertension and bradycardia with non-cardioselective β-blockers.

Note on sotalol

Sotalol, a β-blocker with class III antiarrhythmic effects, has a number of specific interactions, which should be checked before prescribing.

Clinical evidence

- *Angina:* improvement in angina symptoms and exercise tolerance seen in multiple trials: IMAGE (metoprolol, 1996), APSIS (metoprolol, 1996), TIBET (atenolol, 1996), and ASIST (atenolol, 1994).
- *Acute MI mortality:* atenolol shown to reduce acute mortality (ISIS-1, 1986).
- *Post-MI secondary prevention:* reduced mortality and repeat infarction shown in BHAT (propranolol 1982) and Norwegian Multicentre Study Group (timolol, 1981).
- *HF:* use of β-blockers shown to improve survival in those with reduced LVEF from both ischaemic and non-ischaemic aetiology. CIBIS II (bisoprolol, 1999), COPERNICUS (carvedilol, 2001), CAPRICORN (carvedilol, 2001), MERIT-HF (metoprolol, 2000), and SENIORS (nebivolol, 2005).
- *AF:* limited data from randomized trials. AFFIRM (2002) demonstrated that patients treated with β-blockers had similar outcomes to those treated with a rhythm control strategy. Interestingly, an individual patient meta-analysis has shown that the benefits of β-blockers on mortality in HF are not seen in those with AF at baseline.[1]
- *Hypertension:* meta-analyses have concluded that β-blockers do not confer the same stroke protection as other antihypertensive drugs, for the same degree of BP-lowering.[2] β-blockers are no longer recommended early in the treatment of hypertension, unless there is another compelling indication to use them (i.e. post-MI, HF, or angina).

References

1. Kotecha D, Holmes J, Krum H, *et al*. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient meta-analysis. *Lancet*. 2014;**384**:2235–43.
2. Lindholm LJ, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet*. 2005;**266**:1545–53.

Calcium channel blockers: dihydropyridines

Examples in this class

- Amlodipine, felodipine, lacidipine, lercanidipine, nifedipine.

Pharmacology

Mode of action

- CCBs inhibit the inward movement of Ca^{2+} ions through the slow channels located in the cells of the myocardium, the His–Purkinje system, and in vascular smooth muscle.
- DHP-type CCBs have ↑ affinity for vascular smooth muscle, resulting in peripheral vasodilatation, ↓ BP, and ↓ afterload.

Metabolism

- *Liver:* metabolized to inactive metabolites.
- *Excretion:* predominantly renal.
- *Half-life:* amlodipine 30–50h; felodipine 25h; nifedipine 2h.

Indications and place in therapy

- *Angina:* joint first line (equal with β-blockers), may also be used in combination with β-blockers, nitrates, nicorandil, or ivabradine.
- *Hypertension:* ESC guidelines—first-line therapy in combination with ACEis. NICE guidelines—first line for older patients (>55 years) and black patients, can be used in combination with ACEis/ARBs if needed for BP control.

Contraindications and cautions

- *Contraindications:* cardiogenic shock, severe AS, UA.
- *Cautions:* worsening HF.

Usual dosing

- The dose is titrated against response, aiming for adequate BP control in hypertension or symptom resolution in angina management.
- The starting doses and usual dose ranges of commonly prescribed CCBs are summarized in Table 17.13.

Table 17.13 Doses for calcium channel blockers

Agent	Starting dose	Dose range
Amlodipine	5mg daily	5–10mg daily
Felodipine	5mg daily	5–20mg daily
Lacidipine	2mg daily	2–6mg daily
Lercanidipine	10mg daily	10–20mg daily
Nifedipine	20–30mg daily (LA preparation)	30–90mg daily (LA preparation)

Monitoring

- Obtain baseline BP and pulse before initiation and after dose changes.
- If no side effects, review within 4 weeks and consider dose titration.

Adverse effects (selected)

- *Symptomatic hypotension:* consider dose reduction.
- *GI disturbance:* abdominal pain common, may worsen constipation.
- *Gingival hyperplasia:* withdraw CCB and consider alternatives.
- *Headache and flushing:* common in the first 2 weeks, usually resolves over time. Simple analgesics can be used if necessary. Patient hould be reassured and encouraged to continue with therapy.
- *Ankle swelling:* common, often dose-related; consider dose ↓.

Selected interactions

- *Anaesthetics:* enhanced hypotensive effect.
- *Anti-epileptics:* variable effects on CCB plasma levels—consult product literature.
- *Antifungals:* azole group drugs ↑ exposure to CCBs and may precipitate hypotension.
- *Barbiturates:* effect of CCBs reduced.
- *Cimetidine:* ↑ exposure to nifedipine, reduce dose.
- *Mg^{2+}:* IV Mg^{2+} may ↑ risk of hypotension.
- *Mefloquine:* ↑ risk of bradycardia.
- *Other antihypertensives:* ↑ risk of hypotension if co-administered with other agents (e.g. ACEis, α-blockers, β-blockers, thiazide diuretics).
- *Rifampicin:* ↓ exposure to CCBs, avoid co-administration with nifedipine, reduces dose of other DHP CCBs.

Clinical evidence

- *Hypertension:* multiple large-scale randomized studies demonstrated a significant reduction in mortality and morbidity (e.g. ALLHAT, STOP-Hypertension, VALUE).
- *Angina:* reduce frequency and severity of angina episodes. As effective as β-blockers in protecting against effort-induced angina (TIBET, nifedipine, 1996). Reduced revascularizations and hospitalizations for angina (CAMELOT, amlodipine, 2004).

CCBs: non-dihydropyridines

Examples in this class

- Diltiazem, verapamil.

Pharmacology

Mode of action

- CCBs inhibit the inward movement of Ca^{2+} ions through the slow channels located in the cells of the myocardium, the His–Purkinje system, and in vascular smooth muscle.
- The non-DHP-type CCBs have ↑ effect on the myocardium and conduction system, and result in ↓ inotropy, myocardial depression, and AV conduction delay.

Metabolism

- *Liver:* non-DHP CCBs are metabolized to multiple metabolites.
- *Excretion:* non-DHP CCB metabolites mainly renally excreted.
- *Half-life:* 3–4.5h (diltiazem); 3–7.5h (verapamil).

Indications and place in therapy

- *Angina:* first line in patients in whom β-blockers are contraindicated or not tolerated—rate-controlling effects of diltiazem and verapamil may confer an advantage here; may also be used in combination with β-blockers (not verapamil), nitrates, or nicorandil.
- *AF:* may be considered for rate control where first-line options have failed, are contraindicated, or not tolerated.
- *Narrow complex tachycardia:* should be considered if vagal manoeuvres and adenosine fail.

Contraindications and cautions

- *Contraindications:* AV block (second or third degree), bradycardia, cardiogenic shock, LV impairment, porphyria, HFrEF, severe AS, AF/AFl in patients with WPW.
- *Cautions:* after MI (acute phase), elderly patients, first-degree AV block, neuromuscular disease.

Usual dosing

Usually the dose is titrated against response, aiming for a resting HR of 50–60bpm in angina management or <100bpm in AF. Starting and usual doses are summarized in Table 17.14.

Table 17.14 Doses for non-dihydropyridine calcium channel blockers

Agent	Starting dose	Dose range
Diltiazem	Dose depends on formulation and brand	
Verapamil (LA preparation)	120mg daily	240–480mg daily

Monitoring

- Obtain baseline BP and pulse before initiation and after dose changes.
- If no side effects, review within 4 weeks and consider dose titration.

Adverse effects (selected)

- *Bradycardia (HR <50bpm):* consider dose reduction, exclude heart block.
- *Symptomatic hypotension:* consider dose reduction.
- *GI disturbance:* may lead to vomiting or abdominal pain.
- *Gingival hyperplasia:* withdraw CCB and consider alternatives.
- *Headache and flushing:* common in the first 2 weeks and usually resolve over time. Simple analgesics can be used if necessary. Reassure and encourage the patient to continue with therapy.
- *Ankle oedema:* is common, especially with the DHP-type CCBs at higher doses, consider dose reduction.

Selected interactions

- *Anaesthetics:* enhanced hypotensive effect.
- *Antihypertensives:* may potentiate hypotension if co-administered (e.g. with ACEis, α-blockers).
- *AADs:* ↑ bradycardia risk, myocardial depression with amiodarone, risk of asystole when verapamil given with flecainide.
- *Anticoagulants:* dabigatran/edoxaban concentration ↑ by verapamil.
- *Anti-epileptics:* variable effects on plasma levels of both anti-epileptic agent and CCB—consult product literature.
- *Antifungals:* azole group drugs may ↑ exposure to non-DHP CCBs.
- *Antivirals:* atazanavir/darunavir/saquinavir ↑ exposure to non-DHP CCBs.
- *Barbiturates:* effect of non-DHP CCBs reduced.
- *β-blockers:* enhanced hypotensive effect, risk of AV block, bradycardia, severe hypotension, or HF. Avoid with verapamil, closely monitor with diltiazem.
- *Ciclosporin:* plasma levels ↑ by non-DHP CCBs.
- *Clarithromycin:* ↑ exposure to non-DHP CCBs.
- *Colchicine:* ↑ concentration of colchicine by non-DHP CCBs.
- *Eplerenone:* ↑ concentration of eplerenone by non-DHP CCBs.
- *Digoxin:* verapamil ↑ digoxin levels, ↑ risk of AV block/bradycardia.
- *Ivabradine:* plasma level ↑, avoid concomitant use.
- *Lithium:* ↑ risk of neurotoxicity.
- *Magnesium:* may ↑ risk of hypotension.
- *Statins:* plasma level of simvastatin and atorvastatin ↑, ↓ statin dose.
- *Sirolimus/tacrolimus:* plasma levels of these agents ↑ by co-administration. Doses should be adjusted.
- *Ranolazine:* ↑ effect of ranolazine, use with caution.

Clinical evidence

- *AF:* verapamil, diltiazem—multiple small studies demonstrated efficacy in controlling HR at rest/during exercise.
- *Angina:* reduce frequency and severity of angina episodes. As effective as β-blockers in protecting against effort-induced angina (APSIS, verapamil, 1996).

Digoxin

Pharmacology

Mode of action

- Digoxin inhibits Na^+/K^+ ATPase found in the myocardium and cardiac conducting system.
- Blocking this channel ↑ intracellular Na^+; this, in turn, ↑ Ca^{2+} imported by the Na^+/Ca^{2+} antiporter.
- ↑ Ca^{2+} lengthens the cardiac action potential, slowing the HR; it also ↑ the force of contraction.

Metabolism

- *Liver:* minimal liver elimination that only becomes clinically important in renal dysfunction.
- *Excretion:* predominantly renal.
- *Half-life:* 36–48h (if normal renal function), ↑ to up to 5 days in renal dysfunction.

Indications and place in therapy

Atrial fibrillation

- *Rate control:* first-line therapy (β-blockers/non-DHP CCBs are suitable alternatives) in patients with AF requiring rate control.
- *Rhythm control:* digoxin has no role in cardioverting AF.

Heart failure

- Can be considered as an adjunct therapy in symptomatic patients where β-blockers, ACEis/ARBs, and MRAs have all been tried/are contraindicated.

Contraindications and cautions

- *Contraindications:* constrictive pericarditis, HCM, second/third-degree heart block, SVT associated with an AP, ventricular arrhythmias.
- *Cautions:* ↑ Ca^{2+}, ↓ K^+, ↓ Mg^{2+}, hypoxia, recent MI, respiratory disease, sinus node disease, thyroid disease.

Usual dosing

Atrial fibrillation

- *Initiation:* 500–1500mcg in divided doses over 24h.
- *Maintenance therapy:* 62.5–250mcg daily.

Heart failure

- 62.5–125mcg daily.

Monitoring

- Routine monitoring is not required.
- *Suspected toxicity:* an ECG and a digoxin level should be done 8–12h after the last dose (see Box 17.6).
- *Reduced renal function:* digoxin levels should be assessed after dose adjustments.

Box 17.6 Common ECG findings in digoxin toxicity

- Frequent ventricular ectopics: the most common finding in toxicity
- Sinus bradycardia
- Atrial fibrillation—slow
- Heart block
- Ventricular tachycardia
- ST-segment depression: 'reverse-tick'/'scooped-out' morphology is a sign of digoxin use but does not routinely represent toxicity

Adverse effects (selected)

- Arrhythmias, including heart block, GI disturbance, skin reactions, and visual changes.

Selected interactions

Interactions with digoxin primarily relate to ↑ risk of digoxin toxicity. Drugs which may ↑ risk of toxicity include:

- Aminophylline/theophylline
- Amiodarone
- Azole antifungals
- β-adrenergic agonists
- Diuretics (loop and thiazide)
- Corticosteroids
- Macrolide antibiotics
- Non-DHP CCBs.

Clinical evidence

- No head-to-head randomized trials have been performed in AF patients. A meta-analysis of observational data demonstrated no impact on mortality in patients with AF and HF.
- The DIG trial (1997) demonstrated that digoxin, when added to standard HF therapy, demonstrated no change in death but showed a reduction in hospitalization for worsening HF.

Diuretics: loop

Examples in this class

- Bumetanide, furosemide.

Pharmacology

Mode of action

- Act in the ascending limb of the loop of Henle, inhibit Na^+ reabsorption through the Na^+-K^+-$2Cl^-$ cotransporter.

Metabolism

- *Liver:* relatively minimal hepatic metabolism of bumetanide or furosemide.
- *Excretion:* primarily renally cleared.
- *Half-life:* furosemide 100–120min, bumetanide 60–90min.

Indications and place in therapy

- Loop diuretics have profound natriuretic and diuretic effects.
- Principal role in symptomatic management of CCF, both with and without reduced LVEF.
- Furosemide can be given IV in those with acute pulmonary oedema.

Contraindications and cautions

- *Contraindications:* anuria, severe liver cirrhosis, renal failure due to nephrotoxic (or hepatotoxic) agents, hypokalaemia, severe hyponatraemia.
- *Cautions:* gout, hypotension/hypovolaemia, diabetes.

Usual dosing

(See Table 17.15 for usual dosing.)

- In acute pulmonary oedema, IV furosemide dose depends on whether the patient is already using a loop diuretic. If using a diuretic, then the IV dose should be at least equivalent to the PO dose; if diuretic-naïve, then 40mg IV is often used in the first instance.

Table 17.15 Doses for loop diuretics

Agent	Initiation dose	Usual dose range
Bumetanide	1mg od	1mg od to 2mg bd
Furosemide	40mg od	40mg od to 80mg bd

Monitoring

- Renal function and electrolytes should be monitored at baseline, after dose changes, and periodically thereafter.

Adverse effects (selected)

- AKI, dizziness, electrolyte disturbance, headache, metabolic alkalosis.
- *Deafness:* recognized in high doses, with rapid IV administration, and is more common in renal impairment.

Selected interactions

The majority of potentially severe interactions relate to ↓ K^+ associated with loop diuretic use, leading to a higher risk of TdP when given with drugs that prolong the QT interval. These include:

- Azole antifungal agents
- Class Ic AADs: flecainide, procainamide
- Class III AADs: amiodarone/dronedarone
- Haloperidol (and other antipsychotic medications)
- Macrolide antibiotics
- Ranolazine
- SSRIs
- Sildenafil
- Tyrosine kinase inhibitors.

Other selected interactions

- *Lithium:* ↑ concentration of lithium, requires monitoring.

Clinical evidence

- As older medications, loop diuretics have been subjected to few clinical trials.
- Furosemide has been shown to have an ↑ diuretic effect, when compared with thiazide diuretics, but has not been shown to have any benefit on mortality in HF.
- The DOSE trial demonstrated that bolus and infusion administration of furosemide were equivalent in acute pulmonary oedema but showed that higher doses had a non-significant trend towards ↑ improvement in patients’ symptoms.
- Limited evidence comparing the effects of loop diuretics with one another.

Diuretics: thiazide/thiazide-like

Examples in this class

- Thiazide: bendroflumethiazide, hydrochlorothiazide.
- Thiazide-like: indapamide.

Pharmacology

Mode of action

- Inhibits the Na^+-Cl^- cotransporter in the distal convoluted tubule.
- Leads to diuretics and natriuresis, as well as a BP-lowering effect.
- Thiazide drugs have a chemical structure based on benzothiadiazine.
- Thiazide-like drugs do not contain the same chemical structure but inhibit the same transporter in the distal convoluted tubule.

Metabolism

- *Liver:* bendroflumethiazide and indapamide undergo extensive metabolism. Minimal metabolism of hydrochlorothiazide.
- *Excretion:* bendroflumethiazide and indapamide are excreted renally, either unchanged or as a range of metabolites. Hydrochlorothiazide is renally excreted without metabolism.
- *Half-life:* bendroflumethiazide 3–8h; hydrochlorothiazide 6–15h; indapamide 14–18h.

Indications and place in therapy

Hypertension

- Thiazide and thiazide-like diuretics play a central role in management of hypertension. Place in therapy dependent on specific guidelines.
- *ESC:* co-first-line treatment, along with ACEis/ARBs and DHP CCBs. Suggests either thiazide or thiazide-like diuretic use.
- *NICE:* second-line therapy and suggests use of thiazide-like diuretics (i.e. not thiazide diuretics).

Oedema

- Thiazide diuretics can be used as adjunctive therapy for resistant oedema, co-administered with loop diuretics.

Contraindications and cautions

- *Contrainidications:* Addison's disease, ↑ Ca^{2+}, ↓ Na^+, refractory hyperkalaemia.
- *Cautions:* gout, diabetes, hyperaldosteronism (e.g. Conn's syndrome), nephrotic syndrome, lupus.

Usual dosing

(See Table 17.16 for dosing information.)

Table 17.16 Doses for thiazide and thiazide-like diuretics

Agent	Hypertension	Oedema
Bendroflumethiazide	2.5mg od	5–10mg od or on alternate days
Indapamide	2.5mg od	N/A

Hydrochlorothiazide is only available in the UK as a combination tablet with other medications.

Monitoring

- Renal function and electrolytes should be tested at baseline and periodically thereafter.

Adverse effects (selected)

- Electrolyte imbalance, hypersensitivity, hyperuricaemia, hypochloraemic alkalosis, GI disturbance, urticaria.

Selected interactions

The majority of potentially severe interactions relate to ↓ K^+ associated with thiazide diuretic use, leading to a higher risk of TdP when given with drugs that prolong the QT interval. These include:

- Amiodarone
- Haloperidol
- Loop diuretics
- Ranolazine
- Sildenafil
- Tyrosine kinase inhibitors.

Other selected interactions

- *Aspirin/COX inhibitors:* co-administration ↑ risk of AKI.
- *Calcium-containing medications:* ↑ risk of hypercalcaemia.
- *Lithium:* ↑ concentration of lithium, requires monitoring.

Clinical evidence

- Thiazide and thiazide-like diuretics have been shown to reduce mortality, compared with placebo.
- No head-to-head analysis of thiazide vs thiazide-like diuretics have been undertaken.

I_f current inhibitors

Examples of drugs in this class

- Ivabradine.

Pharmacology

Mode of action

- Ivabradine causes as dose-dependent reduction in HR by selective and specific inhibition of the cardiac pacemaker I_f current.
- The I_f current (known as the funny channel) controls spontaneous depolarization in the sinus node and hence regulates HR.
- Usual effect is a 10bpm ↓ in HR at rest and during exercise.
- The ↓ HR leads to ↓ cardiac workload/myocardial oxygen consumption.

Metabolism

- *Liver:* metabolized by the CYP3A4 pathway.
- *Excretion:* both faecal and renal (roughly equal).
- *Half-life:* 11h.

Indications and place in therapy

- *Angina:* ivabradine is indicated as a second-line therapy for chronic coronary syndrome (stable angina) to reduce symptom frequency and improve exercise tolerance where β-blockers, CCBs, and nitrates have been tried or are contraindicated.
- *CCF:* ivabradine should be considered in those with CCF and ↓ LVEF if symptomatic despite β-blockers, ACEis/ARBs, and MRAs.

Contraindications and cautions

- *Contraindications:* sick sinus syndrome, bradycardia (resting HR <60bpm), cardiogenic shock and acute MI, within 4 weeks of CVA, sinoatrial block and third-degree AV block, congenital QT syndrome, pacemaker-dependent patients, UA, pregnancy, and breastfeeding.
- *Cautions:* pre-existing cardiac arrhythmias, concurrent HR-lowering agents, mild HF (NYHA classes I–II), moderate to severe HF (NYHA classes III–IV—SHIFT study), post-CVA, retinitis pigmentosa, hypotension (avoid if BP <90/50mmHg), hepatic insufficiency (avoid if severe), severe renal insufficiency (CrCl <15mL/min).

Usual dosing

- *Initiation:* usually initiated at a dose of 5mg bd.
- *Angina:* after 3–4 weeks, it may be ↑ to 7.5mg bd, if required, for greater symptom control.
- *HF:* after 2 weeks, ↑ to 7.5mg bd if required.
- *Older patients:* if >75 years old or 5mg bd is not tolerated, the dose can be reduced to 2.5mg bd.

Monitoring

- Obtain baseline BP and pulse before initiation and after each change in dose.

Adverse effects (selected)

- *Visual symptoms:* most commonly reported adverse effect. Luminous phenomena occur in 15% of patients, and therefore, new patients should be warned about this potential transient side effect. The possible occurrence of such luminous phenomena should be taken into account when driving or using machinery in situations where sudden variations in light intensity may occur, especially when driving at night. Blurred vision has also been reported.
- *Cardiac conduction effects:* bradycardia, AV first-degree block, and ventricular extrasystoles can occur during therapy.
- *Headache:* generally during early treatment phase.
- *Dizziness:* possibly related to bradycardia
- *GI disturbances:* nausea, vomiting, diarrhoea.

Selected interactions

In general, concomitant use should be avoided with other QT-prolonging agents. Some specific interactions include:

- *Amiodarone:* ↑ risk of TdP and bradycardia
- *Azole antifungals:* ↑ risk of TdP
- *β-blockers:* ↑ risk of bradycardia
- *Digoxin:* ↑ risk of bradycardia
- *Flecainide:* ↑ risk of TdP and bradycardia
- *Haloperidol:* ↑ QT interval, avoid co-administration.
- *Macrolide antibiotics:* ↑ QT interval, avoid co-administration.
- *Sildenafil:* ↑ QT interval, avoid combining with ivabradine.

Clinical evidence

- Clinical studies have shown ivabradine to be as effective as β-blockers in prevention and treatment of angina.
- *Stable angina:* INITIATIVE (2005) randomized patients with stable angina to ivabradine or atenolol. The ivabradine arm showed similar exercise tolerance improvement to that in the atenolol arm. ASSOCIATE (2009) demonstrated improved exercise tolerance with ivabradine over placebo in stable angina.
- *Stable angina with HF:* The BEAUTIFUL (2008) study investigated the role of HR control with ivabradine on top of background therapy, including β-blockers, in the majority in patients with CHD and LVF. It did not find improvement in the primary composite outcome. However, it did show improved outcomes in those with a baseline HR of >70bpm.
- *Stable angina without HF:* SIGNIFY (2014) showed no improvement in CV outcomes when ivabradine was added to standard therapy in those with chronic stable angina without HF.
- *HF outcomes:* SHIFT (2010) showed ↓ hospitalization and CV mortality in HF patients (LVEF <35%).

Inotropes and vasopressors

Examples of drugs in this class

- Adrenaline, dobutamine, milrinone, noradrenaline.

Pharmacology

- *Vasopressors:* agents that principally act to ↑ systemic vascular resistance.
- *Inotropes:* agents that principally act to ↑ cardiac contractility.

Mode of action

- Most inotropes ↑ intracellular Ca^{2+} or sensitivity to Ca^{2+} in the myocardium. This ↑ force of contraction (see Table 17.17).

Table 17.17 Mechanism of action of common inotropes/vasopressors

Agent	Mechanism of action	Effects
Adrenaline Low dose High dose	Effects on all adrenoceptors: Predominantly β agonist Predominantly α agonist	Dose-dependent
Dobutamine	β1 and β2 agonist	↑ myocardial contractility ↓ systemic resistance
Isoprenaline	β1 and β2 agonist	Similar to dobutamine but ↑ heart rate
Levosimendan	Calcium sensitizer	↑ myocardial contractility ↓ systemic resistance
Milrinone	Phosphodiesterase type 3 inhibitor	↑ myocardial contractility ↓ pulmonary vascular resistance
Noradrenaline	α1 agonist	↑ systemic resistance

Metabolism

- Most inotropic agents have very short half-lives (see Table 17.18).

Table 17.18 Pharmacokinetics of inotropic and vasopressor agents

Agent	Onset of action	Half-life
Adrenaline		2min
Dobutamine	1–10min	2min
Isoprenaline		2min
Levosimendan		1h
Milrinone		2h
Noradrenaline		2min

Indications and place in therapy

- Generally indicated in situations where there is acute and reversible insufficiency in CO (inotropes) or systemic vascular resistance (vasopressors).

Contraindications and cautions

- There are few situations where these agents are contraindicated. Most contraindications and cautions are agent-specific.
- Caution with using any agent when hypovolaemia has not been corrected.
- Some selected contraindications and cautions are outlined:
  - *Adrenergic vasopressors:* avoid use in those with phaeochromocytoma or tachyarrhythmia
  - *Dobutamine:* should not be used in septic shock as has inferior outcomes to noradrenaline. Caution in acute HF, acute MI, arrhythmias, HCM, AS, DM, and elderly patients.
  - *Milrinone:* caution in hypokalaemia, HCM, and AS.
  - *Noradrenaline:* avoid in uncontrolled hypertension. Caution in vascular thrombosis, DM, the elderly, or recent MI.

Usual dosing

(See Table 17.19)

Table 17.19 Starting and maximum doses for inotropes/vasopressors

Agent	Starting dose	Maximum dose
Adrenaline	0.01mcg/kg/min	0.1mcg/kg/min
Dobutamine	2mcg/kg/min	20mcg/kg/min
Isoprenaline	1mcg/min	10mcg/min
Levosimendan	12mcg/kg, then 0.05mcg/kg/min	0.2mcg/kg/min
Milrinone	50mcg/kg, then 0.375mcg/kg/min	0.75mcg/kg/min
Noradrenaline	0.01mcg/kg/min	3mcg/kg/min

Monitoring

- These agents should only be used in high-monitoring areas.
- Invasive BP monitoring (e.g. arterial line) is essential.
- A PA catheter has not been associated with improved mortality.
- CVP monitoring may be useful to assess fluid balance.

Lipid-lowering agents: statins

Examples in this class

- Atorvastatin, pravastatin, rosuvastatin, simvastatin.

Pharmacology

Mode of action

- Statins block the action of the enzyme HMG-CoA reductase—this is the rate-limiting step in LDL cholesterol synthesis.
- Statins ↓ total cholesterol, LDL cholesterol, apolipoprotein B, VLDL, and plasma triglycerides (TGs).
- They also ↑ serum concentrations of HDL cholesterol.

For further details, see ➲ Dyslipidaemias: management, pp. 24–5.

Metabolism

- *Liver:* atorvastatin converted into active metabolites.
- *Excretion:* primarily bile/faecal.
- *Half-life:* simvastatin 2h; atorvastatin 14h.

Indications and place in therapy

Primary prevention

- Initiate a generic high-intensity statin (e.g. atorvastatin 20mg daily) in those with ↑ clinical risk and LDL cholesterol above target level.
- LDL cholesterol targets are dependent on underlying risk (see Table 17.20).

Secondary prevention

- Initiate a generic statin (e.g. atorvastatin 40mg daily).
- Intensify therapy in those not achieving targets.
- In ACS, initiate a high-intensity statin (e.g. atorvastatin 80mg daily).

Familial hyperlipidaemia

- Initiate high-intensity statin such as atorvastatin 40mg daily.
- Aim for an LDL cholesterol level of <1.4mmol or ≥50% reduction.
- Likely to require dose titration ± other therapies.

Contraindications and cautions

Contraindications

- Hypersensitivity to individual statins.
- Active liver disease (AST or ALT level >100IU/L) or unexplained persistent isolated elevations in serum transaminase levels.
- Pregnancy and lactation.
- Consideration should be given to delaying statin therapy or addressing contraceptive needs in women of childbearing age.

Cautions

- Hypothyroidism should be corrected before initiation of a statin.
- Patients with a high alcohol intake.
- Patients with risk factors for myopathy or rhabdomyolysis.
- Acute porphyria (rosuvastatin is thought to be safe).
- Renal disease—dose reductions may be necessary.

Table 17.20 Doses for statins

Drug	Usual initiation dose	Dose range
Atorvastatin	20mg daily (40mg if switching from simvastatin 40mg daily)	10–80mg daily
Pravastatin	Usually 40mg once at night	10–40mg daily
Rosuvastatin	5–10mg daily (max. 5mg in Asian patients)	5–40mg daily*
Simvastatin	Usually 40mg daily—but lower dose if drug interactions	10–40mg daily

* Dose of 40mg—specialist use only.

Usual dosing

(See Table 17.20)

Monitoring

Lipid profile

- *Before initiation:* should be tested before starting therapy. In primary prevention, two measurements, 1–12 weeks apart, should be made.
- *After initiation:* recheck 6–8 weeks after initiation or dose ↑.

Liver enzymes

- Check before initiation and after 6–8 weeks (see Box 17.7).

Box 17.7 Management of liver function derangement on statins

ALT <3 times the upper limit of normal

- Continue statin.
- Monitor liver function every 4–6 weeks.

ALT ≥3 times the upper limit of normal

- Stop statin therapy.
- Recheck liver function every 4–6 weeks.
- Consider cautious reintroduction when ALT normalized.

Muscle enzymes

- *Before initiation:* do not start if CK level is >4 times the ULN.
- *After initiation:* routine monitoring not required; only test if clinical features of myopathy.

HbA1c

- Regular monitoring should be considered in those at otherwise high risk of developing diabetes and those on high-dose statin therapy.

Adverse effects (selected)

- *GI disturbance:* advise patient to take with or after food—ideally with their evening meal rather than last thing at night.
- *Insomnia:* take the dose earlier in the day (e.g. with the evening meal or earlier if necessary). Try an alternative statin if problem persists.
- *Muscle aches and pains:* check CK level to exclude myopathy. If no ↑ in CK level, withdraw the agent and rechallenge. If problem recurs, consider an alternative statin.
- *Myopathy:* muscle pains and raised CK level >4 times the ULN indicates myopathy. Statin should be withdrawn, and CK level rechecked. Low doses of less potent statins may be cautiously reintroduced, with careful monitoring under specialist supervision.

Selected interactions

- *Amiodarone:* ↑ risk of myopathy/rhabdomyolysis, ↓ statin dose.
- *Antibacterials:* clarithromycin, daptomycin, erythromycin, and fusidic acid ↑ risk of rhabdomyolysis. Avoid concomitant use.
- *Antifungals:* azole class antifungal agents ↑ risk of myopathy/rhabdomyolysis, and concomitant use should be avoided.
- *Antivirals:* use under specialist supervision only.
- *CCBs:* diltiazem, verapamil—possible ↑ in risk of myopathy, dose reduction required.
- *Ciclosporin:* ↑ risk of myopathy with statins; dose reductions required; avoid concomitant use with rosuvastatin.
- *Colchicine:* ↑ risk of myopathy with statins.
- *Danazol:* possible ↑ in myopathy with simvastatin.
- *Fibrates:* avoid concomitant use of statins with gemfibrozil; ↑ risk of myopathy when other fibrates are used with statins.
- *Grapefruit juice:* plasma concentrations of simvastatin ↑—avoid concomitant use; possible ↑ in plasma concentrations of atorvastatin with excessive intake.
- *Nicotinic acid:* ↑ risk of myopathy with statins.

Clinical evidence

Consistent and robust clinical trial data support the role of statin therapy in CV risk reduction. For further details, see ➔ Dyslipidaemias: management, pp. 24–5.

Adherence issues

- Significant publicity regarding statin adverse effects is associated with the potential for reduced patient adherence to statin therapy.
- In patients failing to respond to statin therapy, compliance issues should be considered and all efforts made to resolve these.
- Fifty per cent of patients stop taking statin therapy within 1 year of initiation, and 75% within 3 years.
- It is essential that patients understand the need for statin therapy to ↓ their long-term risk of CV events, and that once initiated, statins should be continued long term.
- Care should be taken to address adverse effects should they occur, in order to facilitate ongoing adherence.

Lipid-lowering agents: second-line agents

Cholesterol absorption inhibitors

Examples in this class

- Currently only ezetimibe is on the market from this class.

Mode of action

- Interferes with transportation of cholesterol across the brush border in the GI tract, ↓ delivery of intestinal cholesterol to the liver.
- Significant LDL cholesterol ↓, with small ↓ in TGs and ↑ in HDL cholesterol.

Indications and place in therapy

- Should be initiated when target LDL cholesterol is not reached despite maximum tolerated statin dose (ESC Class I recommendation).
- If statins are not tolerated, ezetimibe should be considered in those requiring ↓ LDL cholesterol.

Usual dosing

- 10mg od.

Adverse effects

- Key adverse effects include GI disturbances, headache, and fatigue.
- Myalgia can occur during therapy—check CK level to exclude myopathy.
- *Hypersensitivity:* rash, angio-oedema, and anaphylaxis are reported.

Drug interactions

- Although ezetimibe drug interactions are uncommon, there is an ↑ risk of rhabdomyolysis when ezetimibe and statins are combined.

Clinical evidence

- In IMPROVE-IT, patients were randomized to statin or statin + ezetimibe. The ezetimibe arm had small, but significant, ↓ in CV events (33% vs 35%).

Proprotein convertase subtilisin/kexin 9 inhibitors

Examples in this class

- Alirocumab, evolocumab.

Mode of action

- Monoclonal antibodies which binds to, and inhibit, PCSK9, leading to ↑ LDL receptor expression and ↓ LDL cholesterol concentration.

Indications and place in therapy

- *Primary prevention:* can be considered in those at very high risk if target LDL cholesterol is not reached on statin and ezetimibe.
- *Secondary prevention:* should be used if not reaching target LDL cholesterol on statin and ezetimibe (ESC Class I recommendation).

Contraindications

- History of severe hypersensitivity reaction.

Usual dosing

- Delivered as s/c injection.
- *Alirocumab*: 75mg every 2 weeks, can ↑ to 150mg every 2 weeks.
- *Evolocumab*: 140mg every 2 weeks or 420mg every month.

Adverse effects (selected)

- *Common*: itching at injection site, flu-like symptoms.
- *Rare, but serious:* hypersensitivity vasculitis.

Clinical evidence

- PCSK9 inhibitors ↓ LDL cholesterol levels by an average of 60%.
- Two large trials (FOURIER, ODYSSEY OUTCOMES) demonstrated 15–20% ↓ in composite CVD outcomes in those receiving PCSK9 inhibitors and statins, compared with statins alone.
- The EBBINGHAUS trial was designed to elucidate any neurocognitive functional decline (suggested by FOURIER and ODYSSEY) and was negative.

Fibrates

Examples in this class

- Bezafibrate, ciprofibrate, fenofibrate, gemfibrozil.

Mode of action

- Fibrates activate PPARα, which limits hepatic TG synthesis and ↑ lipoprotein lipase activity, resulting in ↑ LDL cholesterol clearance.
- Fibrates ↓ TGs significantly, but also ↓ LDL and total cholesterol levels.

Indications and place in therapy

- ESC and NICE do not recommend routine use of fibrates for treatment of dyslipidaemias, even when statins are contraindicated.
- In patients with hypertriglyceridaemia (and LDL cholesterol at target), fibrate therapy may be considered in those already on a statin.

Usual dosing

- *Bezafibrate:* 400mg od (modified-release (MR) preparation).
- *Fenofibrate:* 160mg daily (Supralip® preparation).

Adverse effects of fibrates

- Key adverse effects include GI disturbances, which are usually self-limiting, and myositis.

Clinical evidence

- Strong evidence of ↓ in TGs and LDL cholesterol levels.
- Limited evidence supports the use of fibrates to ↓ CV events.
- Although the Helsinki Heart Study demonstrated a ↓ in CV events, this is not supported by other trials (e.g. FIELD, ACCORD).

Lipid-lowering agents: others

Bile acid sequestrants (resins)

Examples in this class

- Colestyramine, colestipol, and colesevelam.

Mode of action

- ↓ enterohepatic circulation of cholesterol by preventing reabsorption from the gut.
- ↓ intestinal reabsorption ↑ LDL receptor activity in the liver, resulting in ↑ clearance of LDL from the plasma.

Usual dosing

- *Colestyramine:* initially 4g daily (max. 36g daily) in 1–4 divided doses.
- *Colestipol:* initially 5g daily (max. 30g daily) in one or two divided doses.
- *Colesevelam:*
  - Monotherapy—3.75mg daily in one or two divided doses
  - With statin—2.5–3.75mg daily in one or two divided doses.

Place in therapy

- Bile acid binders are limited in clinical practice by poor tolerability, drug interactions, and an adverse effect on TG levels.
- Can be considered, in addition to statin therapy, if LDL cholesterol target levels are not reached (ESC Class IIb recommendation).

Adverse effects

- Key adverse effects are GI, including constipation and diarrhoea, nausea and vomiting, and bloating.

Drug interactions (selected)

- *Anticoagulants:* colestyramine may ↑ or ↓ the efficacy of warfarin and other coumarins.
- Bile acid sequestrants may affect the absorption of other medications (e.g. digoxin, thyroid hormones, thiazide diuretics). Other drugs should be taken >1h before/4h after bile acid sequestrants.

Clinical trial data

- Colestyramine showed a trend towards ↓ mortality and non-fatal MI in the LRC-CPP trial; however, there are few other robust outcomes data to support this class.

Nicotinic acid/niacin

Mode of action

- Inhibits diacylglycerol acyltransferase-2 (DGAT-2) enzyme, leading to ↓ secretion of VLDL particles.
- Stimulates ApoA1 production, ↑ HDL.

Place in therapy

- Two large trials (AIM-HIGH, HSP2-THRIVE) showed no beneficial effect of nicotinic acid over statin therapy, but an ↑ in adverse effects.
- Drugs containing nicotinic acid are not licensed in the European Union and have no role in the management of dyslipidaemia.

Renin–angiotensin–aldosterone (RAA) axis: angiotensin-converting enzyme inhibitors

Examples in this class

- Captopril, enalapril, lisinopril, ramipril, perindopril.

Pharmacology

Mode of action

- ACEis block the conversion of angiotensin I to angiotensin II.
- Angiotensin II is a potent vasoconstrictor and promotes the production of aldosterone, which ↑ Na^+ and water retention.
- ACEIs lead to vasodilatation, ↓ systemic BP, and ↓ afterload.

Metabolism

- *Liver:* ramipril is converted to ramiprilat.
- *Excretion:* predominantly renally excreted (except fosinopril, trandolapril, and spirapril).
- *Half-life:* variable—from ≤2h (perindopril) to 13–17h (ramipril).

Choice of agent

- Not all ACEIs are licensed for use in all different CV indications. It is recommended that a licensed agent, with trial evidence to support its use, is chosen for the indication being managed.

Indications and place in therapy

- *Hypertension:* ESC guidelines—suggest should be combined with a CCB in all patients. NICE guidelines—first line in non-black patients aged <55years.
- *HF:* all patients with any degree of LV systolic dysfunction, initiated as soon as possible following diagnosis.
- *Post-MI secondary prevention:* all patients following MI, initiated during the inpatient phase of treatment.
- *CV risk reduction:* patients with CVD (symptomatic or asymptomatic).

Contraindications and cautions

- *Contraindications:* AS/MS, angio-oedema (any cause), hypersensitivity to ACEIs, bilateral renal artery stenosis, pregnancy.
- *Cautions:* hypotension (SBP <90mmHg), patients on high-dose diuretics (i.e. furosemide >80mg daily), breastfeeding, ≥ moderate renal impairment (i.e. creatinine >150micromol/L).

Usual dosing

- *Essential hypertension:* should titrate dose until BP control is achieved, bearing in mind that ↑ ACEi doses confer ↑ CV protection.
- *For other indications (e.g. HF and for cardioprotection in those with, or at risk of, CVD):* the ACEI must be titrated to the target or maximal tolerated dose if the target dose cannot be achieved (i.e. due to hypotension, renal dysfunction, etc.).

See Table 17.21 for initiation and target doses.

Table 17.21 Indications and doses for commonly used angiotensin-converting enzyme inhibitors

Agent	Starting dose	Target dose
Enalapril	2.5–5mg daily	40mg daily (may divide dose)
Lisinopril	2.5–10mg daily, indication-dependent	35–80mg daily
Perindopril	2–4mg od	4–8mg daily, interaction-dependent
Ramipril	1.25–2.5mg daily	10mg daily (may divide dose)

Monitoring

- *Before initiation:* baseline BP and U&Es.
- *After 2 weeks or dose change:* check BP and U&Es, then annually.
- *Renal function decline:* if serum creatinine ↑ >20% (or eGFR ↓ >15%) after initiation, stop ACEi and seek specialist advice.

For criteria prior to ↑ dose, see Box 17.8.

Box 17.8 Prerequisites to increasing angiotensin-converting enzyme inhibitor/angiotensin receptor blocker dose

- Systolic BP >90mmHg
- Serum creatinine ↑ by <20% (or eGFR ↓ <15%) on dose titration
- K^+ <5.5mmol/L

Adverse effects (selected)

- *First-dose hypotension:* use a long-acting agent, avoid excessive diuresis prior to initiation. First dose may be given at night before bedtime to reduce the risk of hypotension and associated falls.
- *Dry cough:* may ↓ if patient persists with therapy. If needed, withdraw agent and reintroduce the same or an alternative ACEi. Consider an ARB if cough recurs/persists.
- *Angio-oedema:* rare, but potentially life-threatening adverse effect. Stop ACEi and seek specialist advice before reinitiation.
- *Rash:* switch ACEi, and if rash persists, consider an ARB.
- *Hyperkalaemia:* advise low-K^+ diet, ensure adequate fluid intake. Reduce dose if K^+ >5.5mmol/L; withdraw ACEi if K^+ >6mmol/L.

Selected interactions

- *Allopurinol:* ↑ risk of hypersensitivity and haematological reactions.
- *Azathioprine:* ↑ risk of anaemia/leucopenia.
- *Ciclosporin:* ↑ risk of hyperkalaemia.
- *Diuretics:* enhances hypotensive effect.
- *Lithium:* ↑ lithium levels.
- *K^+ supplements:* ↑ risk of severe hyperkalaemia.

RAA axis: angiotensin receptor blockers

Examples in this class

- Candesartan, irbesartan, losartan, telmisartan, valsartan.

Pharmacology

Mode of action

- ARBs bind to angiotensin II receptors and therefore block the action of angiotensin II.
- Angiotensin II is a potent vasoconstrictor and promotes the production of aldosterone, which ↑ Na^+ and water retention.
- Unlike ACEis, ARBs do not inhibit the breakdown of bradykinin that is responsible for ACEi-induced cough.

Metabolism

- *Liver:* candesartan cilexetil is a prodrug, which is metabolized by the CYP2C9 pathway into active candesartan. Losartan is metabolized into active metabolites via the CYP2C9 and CYP3A4 pathways.
- *Excretion:* predominantly biliary (losartan and valsartan) or faecal (candesartan).
- *Half-life:* candesartan (9h), valsartan (6h), losartan (2h)—although active metabolites have 6- to 8h half-life.

Choice of agent

- Not all ARBs are licensed for use in all CV indications.
- It is recommended that a licensed agent, with trial evidence to support its use, is chosen for the indication being managed.

Indications and place in therapy

- *Hypertension:* second-line agent after ACEis/CCBs.
- *HF:* second line to ACEis in patients with LV systolic dysfunction, initiated as early as possible following diagnosis.
- *Post-MI HF:* second line to ACEis; valsartan may be considered for patients with post-MI HF.
- *CV risk reduction:* second line to ACEis; telmisartan may be considered in all patients with symptomatic or asymptomatic CVD.

Contraindications and cautions

- *Contraindications:* hypersensitivity to ARBs, pregnancy, breastfeeding.
- *Cautions:* bilateral renal artery stenosis, AS or MS, HCM, prior angio-oedema of any cause, hypotension (SBP <90mmHg), patients on high-dose diuretics (i.e. furosemide >80mg daily), ≥ moderate renal impairment (i.e. creatinine >150micromol/L or eGFR <60mL/min/1.73m^2)—seek specialist advice for initiation.

Usual dosing

- *Essential hypertension:* ↑ dose until BP control is achieved.
- *For other indications (e.g. HF and for cardioprotection in those with, or at risk of, CVD):* the ACEi must be titrated to the target or the maximal tolerated dose if the target dose cannot be achieved (i.e. due to hypotension, renal dysfunction, etc.).

See Table 17.22 for initiation and target doses.

Table 17.22 Indications and doses for commonly used angiotensin receptor blockers

Agent	Starting dose	Target dose
Candesartan:		
Hypertension	8mg daily	8–32mg daily
HF	4mg daily	Up to 32mg daily
Irbesartan	75–150mg daily	Up to 300mg daily
Losartan	50mg daily	50–100mg daily
Telmisartan	40mg daily	Up to 80mg daily
Valsartan:		
Hypertension	80mg daily	Up to 320mg daily
Post-MI HF	20mg bd	Up to 160mg bd

Monitoring

- *Before initiation:* baseline BP and U&Es.
- *After 2 weeks or dose change:* check BP and U&Es, then annually.
- *Renal function decline:* if serum creatinine ↑ >20% (or eGFR ↓ >15%) after initiation, stop ACEi and seek specialist advice.

For criteria prior to ↑ dose, see Box 17.7.

Adverse effects (selected)

- *Symptomatic hypotension:* rare but may occur, particularly if there is intravascular volume depletion. Avoid excessive diuretic doses.
- *Angio-oedema:* has been reported rarely with ARBs. Particular caution should be taken when initiating an ARB in a patient with a history of angio-oedema of any cause.
- *Hyperkalaemia:* more common in those with renal dysfunction. Dose reduction may be required.

Key angiotensin receptor blocker drug interactions

- *Ciclosporin:* ↑ risk of hyperkalaemia.
- *Diuretics:* enhance hypotensive effect.
- *Lithium:* ↑ lithium levels.
- *K^+ supplements:* ↑ risk of severe hyperkalaemia.

RAA axis: aldosterone antagonists

Examples in this class

- Eplerenone, spironolactone.

Pharmacology

Mode of action

- Aldosterone binds mineralocorticoid receptors, ↓ Na^+ and water loss, ↑ BP, ↑ Mg^{2+} and K^+ loss, potentiates sympathetic effects, impairs baroreceptors and endothelial function, and ↑ vascular fibrosis.
- Aldosterone antagonists bind to the aldosterone receptor, ↓ Na^+ reabsorption/K^+ excretion, and antagonize aldosterone effects.

Metabolism

- *Liver:* spironolactone is a prodrug, converted to active metabolites.
- *Excretion:* predominantly urine.
- *Half-life:* eplerenone 4–6h; spironolactone metabolites 14–17h.

Indications and place in therapy

- *Chronic HF:* spironolactone—as an adjunct to standard therapy (ACEi, β-blocker plus diuretic) at low doses in those with ≥ moderate systolic dysfunction.
- *Post-MI HF:* eplerenone—in patients with signs/symptoms of CCF and LV systolic dysfunction. Start within 3–14 days of MI.
- *Hypertension:* consider fourth line in those with resistant hypertension (i.e. on ACEi, CCB, and thiazide diuretic).

Contraindications and cautions

- *Contraindications:* hypersensitivity to aldosterone antagonists, serum K^+ >5.0mmol/L at initiation, ≥ moderate renal insufficiency, anuria, severe hepatic insufficiency.
- *Cautions:* hepatic impairment, renal impairment (avoid if eGFR <50mL/min), pregnancy and lactation, elderly.

Usual dosing

- *Chronic HF:* spironolactone usually initiated at 25mg daily, ↑ to 50mg daily after 4–6 weeks if the patient remains symptomatic. ↓ dose may be required if renal decline, ↑ K^+, or ↓ BP.
- *Post-MI HF:* initiate eplerenone within 3–14 days of acute MI at 25mg daily, increasing to 50mg daily after 4 weeks.

See Table 17.23 for initiation and target doses.

Table 17.23 Doses for commonly used aldosterone antagonists

Agent		Starting dose	Target dose
Spironolactone	*Heart failure*	25mg daily	50mg daily
	Hypertension	100mg daily	25–200mg daily
Eplerenone		25mg daily	50mg daily

Monitoring

- *Before initiation:* baseline BP and U&Es.
- *Within 1 week or dose change:* check U&Es and again after a month.
- Monitoring is recommended at least 3 monthly thereafter.

Adverse effects (selected)

- *Hyperkalaemia:* common. Should avoid high-K^+ foods—bananas, citrus fruit. Dose ↓ or drug withdrawal may be needed (see Table 17.24). Following withdrawal due to ↑ K^+, restart at a dose of 25mg every other day if K^+ is <5.0mmol/L.
- *Renal dysfunction:* renal decline is common following initiation, particularly if already on ACEi/diuretics. Careful fluid balance is essential. May require dose ↓ and, in some cases, drug withdrawal.
- *Gynaecomastia:* can occur with spironolactone. Eplerenone does not affect the progesterone receptor and may be considered as an alternative, although this is unlicensed in chronic HF.
- *GI:* diarrhoea, constipation, nausea, vomiting, and abdominal discomfort have been reported.
- *Menstrual irregularities.*

Table 17.24 Recommended dose adjustments based on potassium levels

Serum K^+ (mmol/L)	Action	Dose adjustment
<5.0	↑ dose	25mg alternate days→25mg daily, 25mg daily→50mg daily
5.0–5.4	No dose adjustment	
5.5–5.9	↓ dose	50mg daily→25mg daily, 25mg daily→25mg alternate days, 25mg alternate days→stop
≥6.0	Stop drug	

Selected interactions

- *ACEis and ARBs:* ↑ risk of severe ↑ K^+ with aldosterone antagonists.
- *α-blockers:* enhanced hypotensive effect.
- *Amiodarone:* plasma levels of eplerenone ↑—↓eplerenone dose.
- *Antibacterial drugs:* plasma levels of eplerenone ↑ by clarithromycin and telithromycin—avoid concurrent use.
- *Anti-epileptic drugs:* plasma levels of eplerenone ↓ by carbamazepine and phenytoin—avoid concurrent use.
- *Antifungal drugs:* itraconazole and ketoconazole ↑ eplerenone levels.
- *Antiviral drugs:* nelfinavir and ritonavir ↑ eplerenone plasma levels—avoid concomitant use; also by saquinavir—↓ eplerenone dose.
- *Cardiac glycosides:* spironolactone may ↑ plasma levels of digoxin.
- *CCBs:* non-DHP CCBs ↑ eplerenone exposure—↓ eplerenone dose.
- *Ciclosporin:* ↑ risk of hyperkalaemia.
- *Lithium:* ↑ lithium levels with associated ↑ risk of toxicity.
- *K^+ salts:* ↑ risk of hyperkalaemia.
- *Tacrolimus:* ↑ risk of hyperkalaemia.

RAA axis: angiotensin receptor–neprilysin inhibitor

Examples in this class

- Sacubitril in combination with valsartan.

Pharmacology

Mode of action

- Sacubitril/valsartan is a combination drug. Valsartan is an ARB (see ➔ RAA axis: angiotensin receptor blockers, pp. 804–5). Sacubitril is a neprilysin inhibitor.
- Neprilysin is an enzyme that degrades BNP, which normally exerts a vasodilatory effect.

Metabolism

- *Liver:* sacubitril is metabolized to LBQ657, which is an active metabolite.
- *Excretion:* majority (50–70%) renal (including active metabolites), and some faecal excretion (30–50%).
- *Half-life:* sacubitril 1–3h.

Indications and place in therapy

- *HF:* in those with LVEF ≤35% who are symptomatic despite maximum tolerated doses of ACEi/ARB, β-blocker, and aldosterone antagonist.

Contraindications and cautions

- *Contraindications:* this medication contains an ARB. As such, it should not be used in combination with either an ACEi or another ARB. Should not be used in SBP <100mmHg.

Usual dosing

- Initiate at 24/26mg bd for 4 weeks and ↑ if tolerated to 49/51mg bd. If tolerated, after a further 4 weeks, consider ↑ to 97/103mg bd.

Monitoring

- As for ARBs (see ➔ Monitoring, p. 805).

Adverse effects (selected)

- Anaemia, cough, GI upset, dizziness/presyncope.

Selected interactions

Interactions with ARBs have been outlined, see ➔ Key angiotensin receptor blocker drug interactions, p. 805. Below is a list of selected interactions for sacubitril.

- *Antihypertensives:* sacubitril ↑ risk of hypotension if used in combination with other antihypertensives.
- *Statins:* sacubitril ↑ exposure to statins. Caution is advised if used in combination.

RAA axis: clinical evidence

Angiotensin-converting enzyme inhibitors

ACEis are supported by a wealth of clinical trial data across a range of indications, including:

- *Hypertension:* numerous clinical studies confirm the BP-lowering efficacy of ACEis.
- *HF* (SAVE (Survival and Ventricular Enlargement), 1993, enalapril; SOLVD (Studies of Left ventricular Dysfunction), 1994, enalapril; ATLAS (Assessment of Treatment with Lisinopril and Survival), 1999, lisinopril). Meta-analyses concluded that ACEis reduce mortality in HF by ~25%, with a substantial reduction in the risk of hospitalization.
- *Post-MI secondary prevention* (AIRE (Acute Infarction Ramipril Efficacy), 1994, ramipril; GISSI-3 (Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico), 1994, lisinopril; ISIS-4, 1994, captopril). ACEis initiated within 24h of presentation reduce the risk of death by ~7%, compared with placebo in the first 4–6 weeks post-MI. In the longer term, mortality is reduced by ~13% in unselected patients, with greater benefits in those with post-MI HF. Long-term follow-up of the SOLVD study showed a significant reduction in all-cause mortality associated with ACEi treatment, even at 12 years post-index event.
- *CV risk reduction* (HOPE (Heart Outcomes Prevention Evaluation), 1999, ramipril; EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease), 2004, perindopril). ACEis have been shown to reduce the risk of CV events in patients who are at high risk of events such as those with established atherosclerotic disease.

Angiotensin receptor blockers

ARBs are supported by fewer clinical trials than ACEIs, but do have data across a range of indications, including:

- *Hypertension:* numerous clinical studies confirm the BP-lowering efficacy of ARBs.
- *HF:* conflicting data emerged from early studies, but CHARM (Candesartan in Heart Failure—Assessment of Mortality and Morbidity) confirmed that candesartan reduced the risk of CV mortality or CV hospitalization in patients with HF, alone or in addition to ACEi therapy, and with or without concurrent β-blocker therapy. (ELITE-II (Evaluation of Losartan in the Elderly), 2000, losartan; ValHeFT (Valsartan Heart Failure Trial), 2001, valsartan; CHARM, 2006, candesartan).
- *Post-MI HF:* valsartan 160mg bd was non-inferior to captopril in protecting against death and CV events in patients with post-MI HF (VALIANT (Valsartan in Acute Myocardial Infarction Trial), 2003).*
- *CV risk reduction:* telmisartan 80mg daily was non-inferior to ramipril 10mg daily in protecting against CV events in patients with CV disease (ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril), 2008).*

(* In these and other studies where ACEis and ARBs have been combined in one of the treatment arms, there has been an i in adverse events (renal dysfunction, symptomatic hypotension, hyperkalaemia), with no demonstrable improvement in outcomes, with the exception of the CHARM study. Therefore, use of an ACEi and an ARB in combination should generally be avoided.)

Aldosterone antagonists

- The landmark trial RALES (Randomized Aldactone Evaluation Study, 1999) secured the place of spironolactone in the management of severe HF (NYHA class IV or class III with recent class IV exacerbation; EF <35%) by demonstrating a 30% reduction in mortality and a 35% reduction in hospitalizations for HF, compared with placebo.
- In the EPHESUS study (2003), eplerenone, initiated in patients with post-MI LV dysfunction (EF <40%) within 3–14 days of the acute event, demonstrated a 15% reduction in the risk of death over the course of 1 year.

Angiotensin receptor–neprilysin inhibitor

- PARADIGM-HF randomized those with HF and LVEF of ≤40% (changed to 35% part-way through the study) and raised BNP level or HF hospitalization to either sacubitril/valsartan or enalapril. Those in the sacubitril/valsartan group had reduced HF hospitalization and overall or CV mortality.

Sodium–glucose cotransporter 2 inhibitors

Examples in this class

- Canagliflozin, dapagliflozin, empagliflozin.

Pharmacology

Mode of action

- These drugs block SGLT2 in the proximal convoluted tubule of the kidney, which prevents glucose reabsorption. This leads to glucosuria and diuresis.

Metabolism

- *Liver:* minimal metabolism for empagliflozin; canagliflozin and dapagliflozin are metabolized by glucuronidation in the liver.
- *Excretion:* empagliflozin and dapagliflozin are predominantly renally excreted; canagliflozin is predominantly faecally excreted.
- *Half-life:* empagliflozin and dapagliflozin 13h; canagliflozin 12h.

Indications and place in therapy

SGLT2 inhibitors are indicated for control of type 2 DM. They have specific benefit in cardiac disease in those with type 2 DM:

- *CAD:* in those with established CAD or at high/very high risk of CAD, SGLT2 inhibitors are recommended as first-line glucose-lowering therapy. Empagliflozin is particularly recommended, as it has been shown to reduce the risk of death.
- *HF:* SGLT2 inhibitors are recommended to reduce the risk of HF hospitalization.

Contraindications and cautions

- *Contraindications:* diabetic ketoacidosis.
- *Cautions*: complicated urinary tract infections, elevated haematocrit, hypotension, risk of volume depletion (including in the elderly).

Usual dosing

- *Canagliflozin:* 100mg od and ↑ up to 300mg od if tolerated.
- *Dapagliflozin:* 10mg od.
- *Empagliflozin:* 10mg od and ↑ up to 25mg od if tolerated.

Monitoring

- *U&Es:* assess before initiation and at least annually thereafter.

Adverse effects (selected)

- Allergic reactions, balanoposthitis, diabetes ketoacidosis, GI reactions, hypoglycaemia, renal failure.
- *Dehydration:* due to diuretic effect of SGLT2 inhibitors. May lead to postural hypotension, dizziness, and syncope.
- *Urinary infections:* inhibition of the SGLT2 channel ↑ glucose in the urine. This is thought to ↑ the risk of urinary infection (including urosepsis). However, data on this adverse effect are conflicting. Fournier's gangrene has also been reported.

Selected interactions

- *Vasodilators:* concomitant use of antihypertensive agents or other vasodilators, use of SGLT2 inhibitors may ↑ the risk of hypotension.
- *Anti-diabetic therapy:* concomitant use ↑ the risk of hypoglycaemia.
- *Rifampicin:* ↓ exposure of canagliflozin, the dose of canagliflozin should be adjusted.

Clinical evidence

- The EMPA-REG OUTCOME trial randomized those with type 2 DM to either empagliflozin or placebo. In the empagliflozin arm, there was a 14% reduced risk of a composite outcome (CV death, MI, or stroke) and a 38% lower risk of CV death. In secondary analyses, there was a 35% lower risk of HF hospitalization in those randomized to empagliflozin.
- Similar findings on composite outcomes were seen in CANVAS and CANVAS-R where participants were randomized to either canagliflozin or placebo.
- Dapagliflozin was shown to reduce the risk of CV death or HF hospitalization by 17% in DECLARE-TIMI 58 but did not reduce a MACE composite outcome.

Enzyme inducers and inhibitors

- Many drugs rely on liver enzymes for their metabolism.
- Drugs which inhibit or induce these enzymes can significantly impact the pharmacokinetics of drugs which are substrates for these enzymes.
- The lists shown in Tables 17.25–17.29 include selective inhibitors and inducers of different liver enzyme pathways.

CYP3A pathway

- This pathway is probably the most important pathway for drug metabolism in humans.

See Table 17.25 for inhibitors and inducers of the CYP3A pathway.

Table 17.25 Inhibitors and inducers of the CYP3A pathway

Classes	Inhibitors	Inducers
Non-cardiac drugs	Azole antifungals Erythromycin Antivirals (e.g. indinavir, ritonavir, saquinavir)	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Rifampicin
Cardiac drugs	DiltiazemVerapamil	Nevirapine Pioglitazone
Other	Grapefruit juice	St John's wort

Cardiac drug substrates for the CYP3A pathway

- *AADs:* amiodarone.
- *Anticoagulants:* warfarin.
- *CCBs, DHP:* amlodipine, felodipine, lercanidipine, nifedipine.
- *CCBs, non-DHP:* diltiazem, verapamil.
- *Statins:* atorvastatin, simvastatin.

CYP1A2 pathway

See Table 17.26 for inhibitors and inducers of the CYP1A2 pathway.

Table 17.26 Inhibitors and inducers of the CYP1A2 pathway

Classes	Inhibitors	Inducers
Non-cardiac drugs	Cimetidine Ciprofloxacin Fluvoxamine	Omeprazole
Cardiac drugs	Amiodarone	
Other		Brussel sprouts Cigarette smoking

Cardiac drug substrates for the CYP1A2 pathway

- *Anticoagulants*: warfarin.

CYP2C9 pathway

See Table 17.27 for inhibitors and inducers of the CYP2C9 pathway.

Table 17.27 Inhibitors and inducers of the CYP2C9 pathway

Classes	Inhibitors	Inducers
Non-cardiac drugs	Fluconazole Isoniazid	Rifampicin Secobarbital
Cardiac drugs	Amiodarone	

Cardiac drug substrates for the CYP2C9 pathway

- *Anticoagulants:* warfarin.
- *ARBs:* irbesartan, losartan.
- *Statins:* fluvastatin.

CYP2C19 pathway

See Table 17.28 for inhibitors and inducers of the CYP2C19 pathway.

Table 17.28 Inhibitors and inducers of the CYP2C19 pathway

Classes	Inhibitors	Inducers
Non-cardiac drugs	Chloramphenicol Cimetidine Ketoconazole Proton pump inhibitors (e.g. lansoprazole, omeprazole, pantoprazole) Oxcarbazepine	Carbamazepine Rifampicin

Cardiac drug substrates for the CYP2C19 pathway

- *Anticoagulants:* warfarin.
- *Antiplatelets:* clopidogrel.
- *β-blockers:* propranolol.

CYP2D6 pathway

See Table 17.29 for inhibitors and inducers of the CYP2D6 pathway.

Cardiac drug substrates for the CYP2D6 pathway

- *β-blockers*: carvedilol, metoprolol, propranolol, timolol.

Table 17.29 Inhibitors and inducers of the CYP2D6 pathway

Classes	Inhibitors	Inducers
Non-cardiac drugs	Celecoxib Cimetidine Selective serotonin reuptake inhibitors (e.g. citalopram, escitalopram, fluoxetine, sertraline, paroxetine) Other antidepressants (e.g. bupropion, clomipramine, duloxetine) Levomepromazine Terbinafine	Rifampicin
Cardiac drugs	Amiodarone Quinidine	

Miscellaneous: QT prolongation

- Many medications prolong the QT interval.
- This can be very important when prescribing in cardiology.
- Prolongation of the QT interval can predispose individuals to developing ventricular arrhythmias.
- Often these effects are additive if multiple QT-prolonging agents are co-prescribed.
- In most cases, the effect on the QT interval is highly variable across individuals.

Cardiac medications with the potential to prolong the QT interval

Below is a selected list of QT-prolonging medications prescribed for patients with cardiac conditions:

- *AADs, class I:* ajmaline, disopyramide, flecainide, procainamide, propafenone, quinidine
- *AADs, class III:* amiodarone, dofetilide, dronedarone, sotalol
- *Antianginals:* ranolazine
- *Thiazide diuretics:* hydrochlorothiazide
- *Thiazide-like diuretics:* indapamide
- *CCBs, DHP:* isradipine, nicardipine.

Non-cardiac medications with the potential to prolong the QT interval

Below is a selected list of QT-prolonging medications not commonly prescribed for cardiac conditions but that may be co-prescribed in such patients:

- *Anti-cancer therapies:* arsenic trioxide, aclarubicin, tacrolimus, tamoxifen
- *Antibiotics:* macrolide and quinolone class antibiotics
- *Antifungals:* co-trimoxazole, fluconazole, ketoconazole, voriconazole
- *Antimalarial agents:* amantadine, chloroquine, hydroxychloroquine, quinine
- *Antipsychotic agents:* haloperidol, risperidone
- *Inotropes/vasopressors:* adrenaline (epinephrine), dobutamine, dopamine, isoprenaline, midodrine, noradrenaline (norepinephrine)
- *Triptans:* naratriptan, sumatriptan, zolmitriptan
- *SSRIs:* citalopram, fluoxetine, paroxetine, sertraline
- *Tricyclic antidepressants:* amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, trimipramine
- *Stimulants:* amphetamine, cocaine, ephedrine, pseudoephedrine, salbutamol, salmeterol
- *Other:* lithium, methadone, domperidone, octreotide, solifenacin, vasopressin.

Complete lists

- The above lists are selected and clinicians are advised to seek up-to-date information on potential effects of medications on the QT interval prior to prescribing.
- An up-to-date list of QT-prolonging medications can be found at: 🖱 www.crediblemeds.org

Chapter 18

Cardiovascular emergencies

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Adult basic life support

- Bystander CPR and use of automated external defibrillators (AEDs) have doubled the chances of survival.
- Basic life support (BLS) is the backbone of effective resuscitation following a cardiorespiratory arrest.
- The algorithm is designed such that BLS may be provided by a bystander in a community or hospital setting. The aim is to maintain adequate ventilation and circulation until further help arrives, the underlying cause for the arrest can be reversed, or return of spontaneous circulation is achieved.

Basic life support algorithm

1. Safety

- *Ensure safety of the rescuer and the patient.*

2. Response

- *Check whether the patient is responsive.* Gently shake the patient and ask loudly '*are you all right?*'.
- If the patient responds, leave them in the position in which you found them, as long as there is no danger in doing so. Reassess frequently.

3. Airway and breathing

- *Open the airway.* Turn the patient onto their back. Place your hand on their forehead. With two fingertips under the point of the chin, gently tilt the head up. If this fails, perform a jaw thrust. Place your fingers behind the angles of the jaw, and apply steady pressure upwards and forwards (see Fig. 18.1).
- *Keep the airway open, and look, listen, and feel for breathing.* Look for chest movements; listen at the patient's mouth for breathing sounds, and feel for air on your cheek.

4. Get help

- If the patient is unresponsive, shout for help (in the community setting, dial 999; ideally stay with the patient, and ask someone else to make the emergency call).
- Send someone to get an AED if there is one available.

5. Circulation

- *Start chest compressions.* Kneel at the patient's side, and place the heel of your hand on the lower half of the patient's sternum and interlock your fingers. Ensure that pressure is applied to the sternum, and not the ribs.
- Keeping your arms straight, apply sufficient pressure to depress the chest by 5–6cm and then release pressure completely.
- Perform 30 chest compressions at a rate of 100–120 compressions per minute followed by rescue breaths.

6. Rescue breaths

- Pinch the soft part of the nose closed.
- Take a normal breath in, and place your lips over the patient's mouth. Blow into their mouth over 1s, and watch to see their chest rise. Take your mouth away, and watch the chest fall. Perform twice.
- Return immediately to 30 chest compressions, and continue with a ratio of chest compressions to rescue breaths of 30:2. If rescue breaths are not performed, compressions should be continuous.

7. Automated external defibrillator

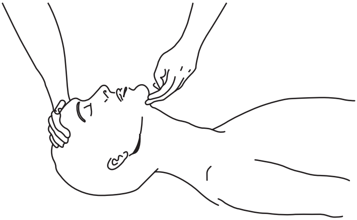
- *If an AED is available.* Attach the pads to the chest. If two people are present, one should continue CPR.
- Follow the spoken and visual instructions.
- Ensure the patient is not touched during rhythm analysis or shock delivery.
- If a shock is warranted, push the button and then resume CPR. If no shock is indicated, immediately continue with CPR.
- Follow the spoken and visual prompts until help arrives.

8. When to stop cardiopulmonary resuscitation

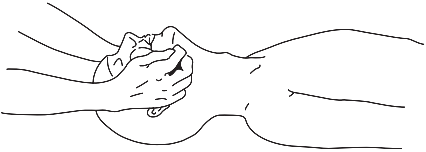
- Do not stop CPR unless you are told by a health professional to do so, you become exhausted, or the patient is moving, opening their eyes, and breathing on their own.

9. Recovery position

- If the patient is unconscious, but breathing normally. Remove glasses if worn, and straighten both of the patient's legs.
- Place the arm that is nearest to you at right angles to their body, bending at the elbow, with their palm facing upwards.
- Bring the other arm across the chest, and put the back of their hand against their cheek.
- Take hold of the leg just above the knee and pull upwards, ensuring the foot is still on the ground. Pull the leg towards you to roll the patient. Ensure that the hip and knee are at right angles.
- Keep the head tilted back to keep the airway open. Check on the patient frequently.



Jaw lift to open the airway



Jaw thrust (thrust the angle of the mandible upwards)

Fig. 18.1 Opening the airways.

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BLS algorithm

Fig. 18.2 shows the BLS algorithm.

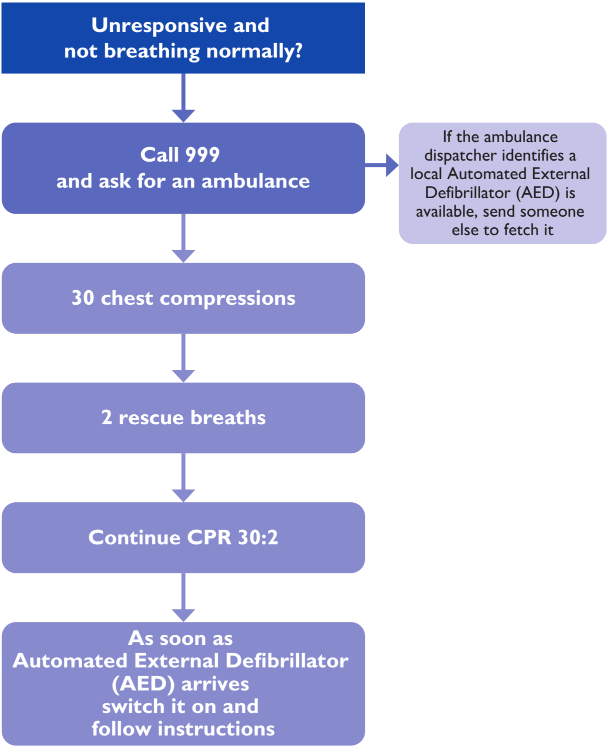
Unresponsive and
not breathing normally?
Call 999
and ask for an ambulance
If the ambulance dispatcher identifies a local Automated External Defibrillator (AED) is available, send someone else to fetch it
30 chest compressions
2 rescue breaths
Continue CPR 30:2
As soon as
Automated External Defibrillator
(AED) arrives
switch it on and
follow instructions

Fig. 18.2 Basic life support algorithm. For further information, see The Resuscitation Council (UK) website (🖱 http://www.resus.org.uk/).

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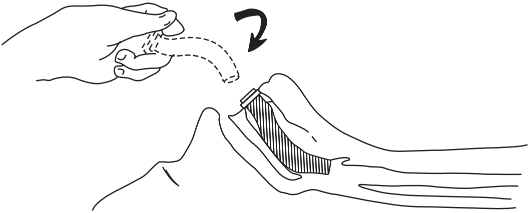
Adult advanced life support: advanced airway management

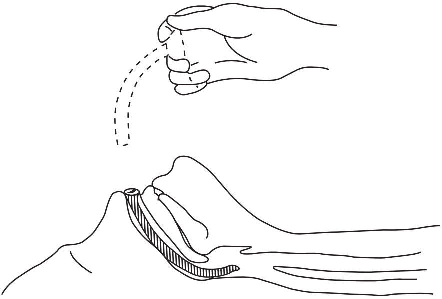
- Advanced life support (ALS) algorithms comprise interventions performed following BLS.
- These include, amongst others, advanced airway management and drug therapies (see ➔ Advanced life support algorithm, p. 828).

Advanced airway management

- Assess the airway as per the BLS algorithm, using a head tilt–chin lift manoeuvre or jaw thrust if required.
- In the prehospital or hospital setting, the airway may be managed by using an oropharyngeal (Guedel) or nasopharyngeal airway. These adjuncts help to maintain the patency of the airway by keeping the tongue out of the way (see Fig. 18.3). A bag–valve–mask can then be attached to deliver oxygen.
- A supraglottic airway (SGA) (e.g. laryngeal mask airway (LMA)) may also be inserted, the most common of which is the I-gel. This comprises a bite block and an oesophageal drain tube, and in contrast to other SGAs, it does not require cuff inflation. This is easy to insert, requiring minimal training and proffers a favourable leak pressure.
- ET intubation is the gold standard for securing the airway but must be performed by a trained individual. Chest compressions should not be paused for longer than 5s in order to pass the tube through the vocal cords. Correct placement should be confirmed clinically through auscultation by waveform capnography.
- *DO NOT ATTEMPT any form of invasive airway management if you are inexperienced*.
- Once an ET tube or SGA is secured, the lungs can be ventilated with the maximal feasible oxygen concentration.
- Each breath should be delivered over 1s at a rate of 10 breaths/min.
- In the case of an unprotected airway, continue CPR at a ratio of 30:2 (see ➔ Basic life support algorithm, p. 822).



Insertion of oropharyngeal airway



Insertion of nasopharyngeal airway

Fig. 18.3 Insertion of a nasopharyngeal airway.

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ALS: shockable/non-shockable rhythms

- Cardiac rhythms of cardiac arrest can be divided into two groups:
  - VF/pulseless VT (pVT)
  - Other cardiac rhythms: asystole and pulseless electrical activity (PEA).
- The principal difference in treatment of the two groups is the need for attempted defibrillation in the VF/pVT group of patients.
- VF/pVT are the first monitored rhythm in 20% of cardiac arrests.
- Fig. 18.4 summarizes the management of both groups of patients.
- PEA occurs where there is cardiac arrest and electrical activity that would normally be associated with a pulse. Survival following PEA/asystole is unlikely unless a reversible cause can be found.

Treatment of shockable rhythms (ventricular fibrillation/pulseless ventricular tachycardia)

1. Confirm cardiac arrest (look, listen, and feel for breathing, and simultaneously palpate the carotid pulse for 10s).
2. Dial for the resuscitation team.
3. Commence the BLS algorithm (see ➔ Basic life support algorithm, p. 822).
4. Secure the airway (see ➔ Advanced airway management, p. 824).
5. Establish vascular access as soon as possible (peripherally or centrally). If IV access fails, an interosseous route should be pursued.
6. Place pads whilst performing CPR, one below the right clavicle and the other at the level of V6 in the mid axillary line. In a resuscitation team, stages 3–6 may be performed simultaneously.
7. Stop compressions for ≤5s to confirm the rhythm.
8. Resume CPR. Ask others to stand away, and remove oxygen.
9. Charge the defibrillator to ≥150J. Once charged, ask the person doing chest compressions to stand clear.
10. Deliver the shock and immediately resume CPR (≤5s delay between the shock and resuming CPR). It is very uncommon for a pulse to be felt immediately and this should not be attempted.
11. Continue for 2min.
12. Recheck the rhythm. If still shockable, repeat stages 8–10.
13. Recheck the rhythm. If this is again shockable, repeat stages 8–10.
14. Give 1mg IV adrenaline and 300mg IV amiodarone, whilst performing a further 2min of CPR. Drug delivery should be followed by a 20mL flush and, if peripheral access, extremity elevation to ensure central drug delivery. Do not administer adrenaline if there are signs of return of spontaneous circulation (ROSC).
15. Repeat stages 8–10 each time a shockable rhythm is identified. Give 1mg IV adrenaline after alternate shocks (every ~3–5min).
16. Consider further 150mg amiodarone IV after five shocks.
17. If there is CO and an organized electrical rhythm, look for ROSC—check for signs of life such as purposeful movement, normal breathing or coughing, central pulse, and end-tidal carbon dioxide.
18. If ROSC, start post-resuscitation care.
19. If rhythm not VF/pVT and no ROSC, switch to non-shockable pathway (see ➔ Treatment of non-shockable rhythms, p. 827).

Witnessed and monitored ventricular fibrillation/pulseless ventricular tachycardia

- Confirm cardiac arrest.
- If the rhythm is shockable, three successive ('stacked') shocks may be given. Assess for a rhythm change and ROSC following each shock.
- If not successful, continue CPR and treat stacked shocks as a first shock.
- Although stacked shocks are not supported by data, it is assumed that early defibrillation, rather than CPR, will ↑ the chance of ROSC.

Precordial thump

- Unlikely to cardiovert a shockable rhythm, not routinely recommended but may be considered when it does not delay defibrillation.
- Use the ulnar edge of a clenched fist to deliver a sharp impact to the lower half of the sternum from 20cm. Retract the hand immediately.

Treatment of non-shockable rhythms (pulseless electrical activity/asystole)

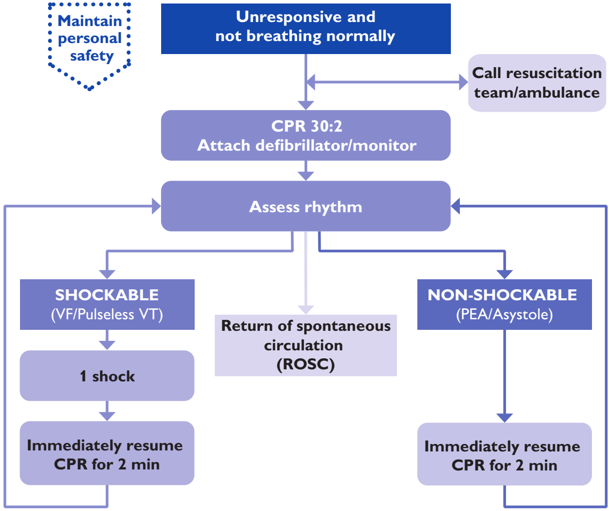
1. Confirm cardiac arrest (look, listen, and feel for breathing and simultaneously palpate the carotid pulse for 10s).
2. Call for the resuscitation team if a cardiac arrest is confirmed.
3. Commence the BLS algorithm (see ➔ Basic life support algorithm, p. 822).
4. Secure the airway, see ➔ Advanced airway management, p. 824.
5. Establish vascular access as soon as possible (peripherally or centrally). If IV access fails, an interosseous route should be pursued.
6. Place pads whilst performing CPR, one below the right clavicle and the other at the level of V6 in the mid-axillary line. In a resuscitation team setting, stages 3–6 may be performed simultaneously.
7. Stop compressions for ≤5s to confirm rhythm.
8. If the rhythm is not shockable, continue CPR for 2min.
9. Recheck rhythm. If electrical activity is compatible with life, check the pulse. If a pulse is palpable with signs of life, commence post-resuscitation care. If no pulse/signs of life, continue CPR.
10. Recheck the rhythm at 2min.
11. Give 1mg IV adrenaline every other CPR cycle (every ~3–5min).
12. If VF/pVT at rhythm check, switch to the shockable algorithm.

If there is evidence of P waves during the rhythm check, it may be possible to pace the patient, even if there is ventricular standstill.

Changes from 2010 guidelines

- Limit interruption to chest compressions ≤5s for defibrillation or intubation. In the former case, the individual performing chest compressions continues to do so as the defibrillator is charged.
- Waveform capnography can be used to monitor ET tube placement and the quality of CPR, as well as ROSC.
- Mechanical chest compression, although not routinely recommended, may be used where manual compression is not possible.
- Periarrest US may help to determine the causes of cardiac arrest.
- Consider the use of ECLS techniques.

ALS algorithm


Maintain personal safety
Unresponsive and not breathing normally
Call resuscitation team/ambulance
CPR 30:2
Attach defibrillator/monitor
Assess rhythm
SHOCKABLE
(VF/Pulseless VT)
Return of spontaneous circulation (ROSC)
NON-SHOCKABLE
(PEA/Asystole)
1 shock
Immediately resume CPR for 2 min
Immediately resume CPR for 2 min

Give high-quality chest compressions, and:
- Give oxygen
- Use waveform capnography
- Continuous compressions if advanced airway
- Minimise interruptions to compressions
- Intravenous or intraosseous access
- Give adrenaline every 3–5 min
- Give amiodarone after 3 shocks
- Identify and treat reversible causes

Identify and treat reversible causes
- Hypoxia
- Hypovolaemia
- Hypo-/hyperkalaemia/metabolic
- Hypo/hyperthermia
- Thrombosis – coronary or pulmonary
- Tension pneumothorax
- Tamponade – cardiac
- Toxins

Consider ultrasound imaging to identify reversible causes

Consider
- Coronary angiography/percutaneous coronary intervention
- Mechanical chest compressions to facilitate transfer/treatment
- Extracorporeal CPR

After ROSC
- Use an ABCDE approach
- Aim for SpO_2 of 94–98% and normal $PaCO_2$
- 12-lead ECG
- Identify and treat cause
- Targeted temperature management

Fig. 18.4 Advanced life support treatment algorithm. For further information, see The Resuscitation Council (UK) website (✎ http://www.resus.org.uk/).

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ALS: reversible causes

- During resuscitation, it is important to consider potential reversible causes. These are divided into two groups: the four Hs and the four Ts.

The four Hs

Hypoxia

- Maximize oxygen delivery during resuscitation.
- Check ET tube placement is correct.

Hypovolaemia

- Restore intravascular volume with fluid/blood products as required.

Hyper-/hypokalaemia, hypoglycaemia, hypocalcaemia, or other metabolic disorders

- Correct electrolyte abnormalities.
- Give IV calcium chloride in the case of hyperkalaemia.

Hypothermia

- May be suggested by the history (e.g. cardiac arrest caused by drowning).

The four Ts

Thrombosis

- ACS is usually diagnosed post-ROSC.
- If ACS is strongly suspected without ROSC, urgent coronary angiography ± PCI should be considered.
- In the case of PE, a fibrinolytic drug should be administered immediately.
- If a fibrinolytic drug is administered, CPR should continue following this for at least 60–90min before termination of resuscitation attempts.

Tension pneumothorax

- This is usually diagnosed clinically and in the arrest setting, usually following trauma.
- This can be decompressed by using needle thoracocentesis and a chest drain inserted.

Tamponade

- This is most commonly diagnosed on US.
- This can be treated with pericardiocentesis in the acute setting.

Toxins

- This may be suggested by the history or following toxicology testing.
- If possible, antidotes should be promptly administered.

ALS: post-resuscitation care

- Aims are to adequately monitor and stabilize the patient, and establish an arrest aetiology (see Fig. 18.5).
- Manage the patient in the appropriate setting (CCU, HDU, or ICU).

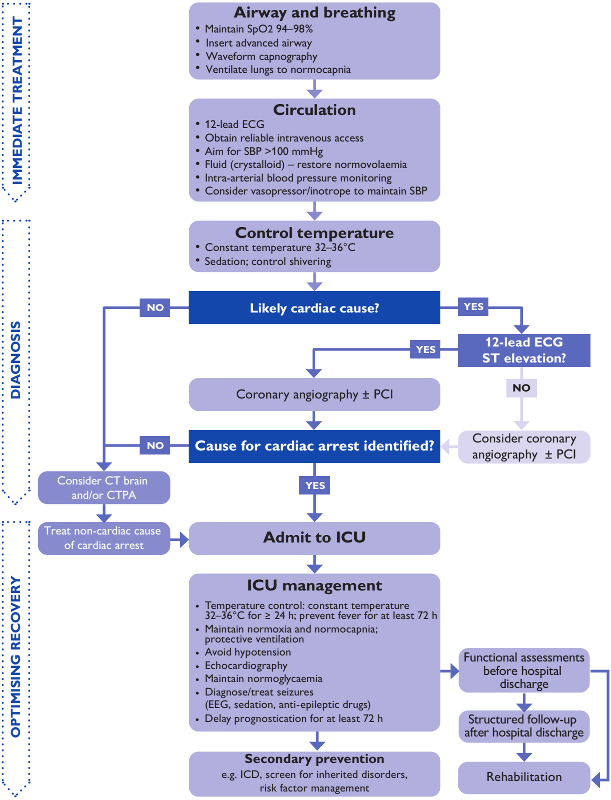
IMMEDIATE TREATMENT
DIAGNOSIS
OPTIMISING RECOVERY
Airway and breathing
• Maintain SpO2 94–98%
• Insert advanced airway
• Waveform capnography
• Ventilate lungs to normocapnia
Circulation
• 12-lead ECG
• Obtain reliable intravenous access
• Aim for SBP >100 mmHg
• Fluid (crystalloid) – restore normovolaemia
• Intra-arterial blood pressure monitoring
• Consider vasopressor/inotrope to maintain SBP
Control temperature
• Constant temperature 32–36°C
• Sedation; control shivering
NO
Likely cardiac cause?
YES
12-lead ECG ST elevation?
YES
NO
Coronary angiography ± PCI
Consider coronary angiography ± PCI
NO
Cause for cardiac arrest identified?
YES
Consider CT brain and/or CTPA
Treat non-cardiac cause of cardiac arrest
Admit to ICU
ICU management
• Temperature control: constant temperature 32–36°C for ≥ 24 h; prevent fever for at least 72 h
• Maintain normoxia and normocapnia; protective ventilation
• Avoid hypotension
• Echocardiography
• Maintain normoglycaemia
• Diagnose/treat seizures (EEG, sedation, anti-epileptic drugs)
• Delay prognostication for at least 72 h
Functional assessments before hospital discharge
Structured follow-up after hospital discharge
Rehabilitation
Secondary prevention
e.g. ICD, screen for inherited disorders, risk factor management

Fig. 18.5 Post-resuscitation care. For further information, see The Resuscitation Council (UK) website (🖱 http://www.resus.org.uk/).

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Airway and breathing

- Patients not requiring intubation/ventilation may still need oxygen.
- ↑ oxygen may lead to ↓ outcomes following MI and may worsen neurological outcomes. Therefore, post-arrest oxygen saturation should be titrated to between 94% and 98%.
- Individuals who have depressed cerebral function should be intubated and ventilated to establish normocapnia. They should be given sedation in order to reduce oxygen consumption.
- A gastric tube should be inserted to decompress the stomach. Gastric distension may occur due to mouth-to-mouth/bag–mask ventilation.
- Ensure a CXR is performed in order to check the position of the ET tube and gastric tube, as well as central venous access.

Circulation

- An ECG should be performed to assess for arrhythmias/ischaemia.
- Blood tests provide important information on clotting, blood count, electrolytes, organ function, toxins, and infection. Reversible abnormalities (e.g. electrolytes) should be corrected immediately.
- Acid–base status may be assessed using ABG sampling.
- Suitable IV access should be obtained, and an arterial line inserted.
- The patient should be catheterized to monitor urine output.
- Fluid status should be monitored by using other physiological indicators such as HR, BP, and acid–base status.
- Early echocardiography should be performed in order to detect myocardial dysfunction and guide fluid resuscitation/inotropic support.
- Coronary angiography and intervention may be considered.

Optimizing neurological recovery

- Seizures are common post-cardiac arrest and therefore, it may be useful to use electroencephalography (EEG). Seizures should be treated promptly as they may exacerbate brain injury.
- Avoid hyperglycaemia, and aim to keep blood glucose levels <10mmol/L. Strict glucose control may lead to hypoglycaemia and should be avoided.
- Temperature should be maintained at 32–36°C in those who remain unresponsive after ROSC. Temperature should be controlled for ≥24h. May be achieved by several methods (e.g. ice packs/wet towels, cooling blankets, intravascular heat exchanger).

Additional investigations and further management

- If there is no coronary cause of cardiac arrest, CT brain and CT chest/CTPA should be considered. Consider ICD implantation, family screening, and physical and psychological rehabilitation.

Organ donation

- Prognostication should be delayed until 72h after cardiac arrest.
- Those who fulfil the criteria for death by using neurological criteria could be considered for organ donation following circulatory death.

Acute coronary syndrome: acute management

See ➔ Chapter 1 for further information. Acute management is briefly as follows.

Investigations

- *Bloods:* clotting, FBC, U&Es, LFTs, glucose, CRP, troponin, lipids, glucose.
- *ECG:* perform within 10min. Attach ECG monitoring, ideally with defibrillator capacity, to the patient.
- *CXR:* identification of pulmonary oedema/pulmonary pathology.
- *Echocardiography:* should be performed for diagnostic purposes but must not delay PCI if indicated.

Management

- Immediate assessment of airway, breathing, and circulation.

Airway management

- Routine oxygen is not recommended if oxygen saturation ≥90%—hyperoxia may be harmful. In patients with refractory pulmonary oedema, CPAP or ET intubation may be necessary.

Initial pharmacological management

- Administer pain relief as a priority.
- In patients with NSTEMI/UA, early use of a β-blocker and S/L or IV nitrates should be considered.
- In patients with STEMI, pain relief is most commonly provided by IV morphine. Nausea and vomiting should be treated with metoclopramide (10mg IV).
- Load the patient with aspirin 300mg PO and ticagrelor 180mg PO or prasugrel 60mg PO. Patients previously taking clopidogrel should be loaded on ticagrelor, irrespective of this, unless contraindicated.
- Prasugrel should not be used in patients aged ≥75 years, weighing <60kg, or with previous CVA/TIA as there is no clinical benefit in these individuals.
- If ticagrelor/prasugrel are contraindicated, the patient is already on PO anticoagulation, or unavailable, load with clopidogrel 600mg PO.
- Administer acute anticoagulation. Agents include UFH, fondaparinux, or LMWH—be guided by your trust protocols. In those individuals undergoing immediate PCI, anticoagulation may alternatively be administered once in the catheter laboratory.

(See ➔ ACS: emergency drugs, p. 64 for further information on pharmacotherapy.)

Glucose control

- Glycaemic status should be evaluated in all patients maintaining blood sugar levels at ≤11mmol/L whilst avoiding hypoglycaemia.
- Glucose-lowering therapy should be considered in those who have glucose levels >10mmol/L.
- Less stringent control should be considered in those who have advanced CVD, are older, and have greater number of comorbidities.

Emergency drugs for ACS

See ➔ ACS: immediate management, pp. 62–3 for administration protocol.

Table 18.1 lists the common drugs administered during ACS and their doses.

Table 18.1 Doses of common drugs administered during acute coronary syndrome

Drug	Dose
Antiplatelet agents	
Aspirin	Loading dose of 300mg PO followed by 75mg od
Clopidogrel	Loading dose of 300 or 600mg PO followed by 75mg od
Ticagrelor	Loading dose of 180mg PO followed by 90mg bd
Prasugrel	Loading dose of 60mg PO followed by 10mg od
Abciximab	Bolus of 0.25mg/kg IV and 0.125mcg/kg/min infusion (max. 10mcg/min) for 12h
Tirofiban	25mcg/kg over 3min IV followed by 0.15mcg/kg/min over 18h
Anticoagulants	
Unfractionated heparin	70–100IU/kg IV when not given with a GPIIb/IIIa inhibitor; 50–70IU/kg IV bolus with GPIIb/IIIa inhibitor
Enoxaparin	1mg/kg s/c bd
Fondaparinux	2.5mg s/c od
Bivalirudin	100mcg/kg bolus IV followed by single dose of 500mcg/kg; then 1.75mg/kg/h for duration of procedure, reduced to 250mcg/kg/h for 4–12h as necessary
Fibrinolytic agents	
Alteplase	15mg IV bolus, 0.75mg/kg IV over 30min (up to 50mg) followed by 0.5mg/kg IV over 60min (up to 35mg)
Reteplase	10 units +10 units IV given at 0 and 30min
Tenecteplase	Single IV bolus based on weight
Nitrates	
Isosorbide dinitrate	1mg/h, ↑ to 10mg/h

Complications post-ACS

Pericarditis (see ➲ Pericarditis)	p. 81
Pericardial effusion (see ➲ Pericardial effusion with or without tamponade)	pp. 298–9
Pulmonary embolism (see ➲ Pulmonary thromboembolism)	p. 81
VSD (see ➲ Ventricular septal defect post-MI)	pp. 82–3
Acute MR (see ➲ Acute mitral regurgitation post-MI)	p. 83
Acute HF (see ➲ Acute heart failure)	p. 84
Cardiogenic shock (see ➲ Cardiogenic shock)	p. 84
RV infarction (see ➲ Right ventricular infarction)	p. 85
Pseudoaneurysm and free wall rupture (see ➲ Pseudoaneurysm and free wall rupture)	p. 85
Thrombosis (see ➲ Thrombosis)	p. 87
Fever (see ➲ Fever)	p. 87
Cocaine-induced MI (see ➲ Cocaine-induced myocardial infarction)	p. 65
Ventricular tachyarrhythmias (see ➲ Ventricular tachyarrhythmias post-MI)	p. 86
Atrial tachyarrhythmias (see ➲ Atrial tachyarrhythmias post-MI)	p. 86
Bradyarrhythmias (see ➲ Bradyarrhythmias)	p. 86

Acute heart failure

See ➔ Management of acute heart failure, pp. 108–11.

Investigations

- *Bloods:* FBC, U&Es, LFTs, TFTs, glucose, NT-proBNP, septic screen (CRP, blood cultures) if pyrexial, D-dimer if possible PE.
- *ABG:* if hypoxic, otherwise venous blood gas (VBG) in individuals with no indication for ABG to assess pH and lactate.
- *ECG:* may identify ischaemia and arrhythmias.
- *CXR:* to look for pulmonary congestion, as well as identify non-cardiac causes of deterioration.
- *Echocardiography:* assessment of structural causes of HF.

Management

- Immediate assessment of airway, breathing, and circulation.

Airway management

- Oxygen should only be used in hypoxic patients where SpO_2 is <90% or PaO_2 is <8kPa, and can be ↑ to FiO_2 of 100% unless other contraindications (e.g. COPD).
- NIV (CPAP, BiPAP) should be considered in patients demonstrating signs of respiratory distress such as RR >25bpm or SpO_2 <90%. BP may ↓ on NIV initiation. Intubation is indicated if PaO_2 <8kPa, $PaCO_2$ >6.65kPa, and pH <7.35 despite NIV.

Initial pharmacological management

- IV diuretics can be given as a bolus dose or a continuous infusion (20–40mg for those who are diuretic-naïve and at least the equivalent PO dose for those already on diuretic therapy).
- If BP >110mmHg, consider IV vasodilators (e.g. GTN). Patients may develop headache and tolerance with prolonged use.
- Patients with AF and a ventricular rate >110bpm should be loaded with digoxin (250–500mcg) PO/IV, with a second dose 6h later and then a PO maintenance dose of 62.5mcg or 125mcg od. Amiodarone may also be considered.

Inotropes

- Inotropes should be considered if the patient has a BP of <90mmHg, with a CO resulting in organ hypoperfusion and the cause is felt to be reversible (see Table 18.2). First-line inotropic therapy is usually dobutamine. Inotropes should be used with caution in patients with tachycardia (>100bpm), as they may exacerbate or precipitate arrhythmias.
- Vasopressors (e.g. noradrenaline, dopamine) should be added to therapy in patients who are still in cardiogenic shock (BP <90mmHg) despite inotropic support to augment BP.

Ultrafiltration

- Indicated if K^+ >6.5mmol/l, pH <7.2, urea >25mmol/L, or creatinine >300micromol/L.

Mechanical support

- IABP may be indicated with acute mechanical issues (ventricular rupture, acute MR), severe myocarditis, or peri-procedure in the case of acute myocardial ischaemia. VADs may act as a bridge to decision in some patients.

Table 18.2 Emergency drug doses for acute heart failure

Drug	Bolus dose	Infusion
Inotropes		
Dobutamine (β receptor agonist)	None	2–20mcg/kg/min
Dopamine (β receptor agonist)	None	3–5mcg/kg/min
Levosimendan	Optional 12mcg/kg over 10min	0.1mcg/kg/min, which can be halved or doubled
Milrinone	25–75mcg/kg over 10–20min	0.375–0.75mcg/kg/min
Vasopressors		
Noradrenaline	None	0.2–1mcg/kg/min
Adrenaline	During resuscitation (see ➔ ALS: Shockable/non-shockable rhythms, pp. 826–7)	

Pulmonary oedema

Non-cardiac causes of pulmonary oedema are listed in Box 18.1.

Box 18.1 Non-cardiac causes of pulmonary oedema

Increased pulmonary capillary pressure (hydrostatic)	
Left ventricular end-diastolic pressure	• Fluid overload • High-output states (anaemia, thyrotoxicosis, Paget's disease, arteriovenous fistula, beri-beri) • Renovascular disease
Pulmonary venous pressure	• Left-to-right shunt (e.g. ventricular septal defect) • Veno-occlusive disease
Neurogenic	• Intracranial haemorrhage • Cerebral oedema • Post-ictal
High-altitude pulmonary oedema	
Increased pulmonary capillary permeability	
Acute lung injury	• Acute respiratory distress syndrome
Decreased intravascular oncotic pressure	
Hypoalbuminaemia	• ↑ losses (e.g. nephrotic syndrome, liver failure) • ↓ production (e.g. sepsis) • Dilution (e.g. crystalloid transfusion)

Tachyarrhythmias

See ➔ Chapter 3 for further information.

- Assessment of airway, breathing, and circulation.
- Oxygen should be administered to hypoxic patients.
- IV access should be gained and bloods taken, including clotting, Hb, U&Es, LFTs, glucose, CRP, troponin, glucose, K^+, Mg^{2+}, and Ca^{2+}.
- An ABG/VBG may be also useful for rapid assessment of acid–base status.
- A 12-lead ECG should be obtained, where possible, to further assist in identification of the underlying rhythm.

Unstable patients

- Unstable patients are those in shock or who have had syncope, myocardial ischaemia, and HF.

Synchronized cardioversion

- Synchronized cardioversion is recommended if unstable.
- This should be carried out under sedation/general anaesthesia unless the patient is unconscious.
- The defibrillator should be set to synchronized mode.
- Start at 120–150J for AF or broad complex tachycardia, and ↑ if this fails (up to three attempts).
- Start at 70–120J for AFl and narrow complex tachycardias (up to three attempts).
- If cardioversion fails, the patient should be given 300mg IV amiodarone and have one further attempt at DCCV. The bolus dose of amiodarone should be followed by 900mg IV over 24h.

Broad complex tachycardia (QRS >120ms)

Regular broad complex tachycardia

Differential diagnosis

- VT.
- SVT with aberrancy.
- *In an unstable patient, always assume that this is VT.*

Management

- Low threshold to undertake synchronized cardioversion.
- 300mg IV amiodarone over 20–60min followed by 900mg IV over 24h.
- If this is known to be SVT with aberrancy, follow the pathway for management of narrow complex tachycardia (see ➔ Algorithm for management of tachyarrhythmias, p. 843).

Irregular broad complex tachycardia

Differential diagnosis

- AF with aberrancy.
- Pre-excited AF.
- Polymorphic VT (TdP).

Management

- Do not give IV amiodarone for TdP. Stop all QT-prolonging medications. Correct electrolyte abnormalities. Give 2g IV magnesium sulfate over 10min.

- Treat AF with BBB as for narrow complex tachycardia (see ➲ Algorithm for management of tachyarrhythmias, p. 843).
- Consider amiodarone for pre-excited AF. This is in contrast to the ESC guidelines which recommend the use of flecainide. If this is known to be SVT with aberrancy, follow the pathway for management of narrow complex tachycardia (see ➲ Algorithm for management of tachyarrhythmias, p. 843).
- Avoid adenosine, diltiazem, verapamil, and digoxin in those with pre-excited AF, as these drugs block the AVN and can cause an ↑ in pre-excitation.

Narrow complex tachycardia (QRS <120ms)

Regular narrow complex tachycardia

Differential diagnosis

- Sinus tachycardia.
- AVNRT.
- AVRT.
- AFl (with regular AV conduction).

Management

- Rule out sinus tachycardia which represents a non-cardiac issue.
- Vagal manoeuvres (terminate up to 25% of paroxysmal SVTs).
- It is important to record an ECG whilst performing vagal manoeuvres or otherwise attempting to convert the arrhythmia, in order to document the response.
- If vagal manoeuvres are not effective, then give adenosine 6mg IV (caution: bronchospasm/AV block).
- If no response, give a 12mg bolus, and again with a 18mg bolus.
- AVNRT or AVRT should terminate. Failure to terminate is suggestive of atrial tachycardia.
- If adenosine cannot be given or fails to terminate the tachycardia, consider verapamil 2.5–5mg IV.

Irregular narrow complex tachycardia

- AF/AFl with variable AV conduction.

Management

- Consider rate control with a β-blocker. Diltiazem or verapamil may be used in patients in whom β-blockers are contraindicated, but should not be used in those with known LV impairment. Digoxin may be used in patients with HF.
- Can consider rhythm control, with either DCCV or chemical cardioversion with amiodarone. Patients who have been in AF for >48h should not undergo cardioversion, unless they have been anticoagulated for at least 3 weeks or TOE shows there is no clot in the LAA. In patients in AF for <48h, a single weight-adjusted dose of LMWH should be given. UFH with a subsequent infusion may be considered as an alternative.

See ➲ Chapter 3 for further information.

Emergency drugs for tachyarrhythmias

Table 18.3 shows the emergency drugs for tachyarrhythmias and their doses.

Table 18.3 Emergency drug doses for tachyarrhythmias

Drug	Dosage
Magnesium sulfate	Loading dose 8mmol (2g) IV over 10–15min
Lidocaine	Loading dose 100mg IV over 2min (repeat once if necessary) Maintenance dose 4mg/min for 30min, 2mg/min for 2h, and 1mg/min for up to 24h. Dose should be reduced if continued beyond this
Amiodarone	Loading dose 300mg IV over 20–60min followed by 900mg IV over 23h or 200mg PO tds × 1 week, then 200mg PO bd × 1 week, then 200mg PO od Maintenance dose 200mg od PO
Flecainide	Loading dose 2mg/kg IV over 10min (max. 150mg) Maintenance dose 1.5mg/kg IV over 1h, then 100–250mcg/kg/h IV for 24h or 100–200mg PO bd
Digoxin	Loading dose: 0.75–1mg IV over 2h, 0.75–1.5mg PO in divided doses over 24h doses Maintenance dose: 62.5–250mcg daily (IV or PO)
Metoprolol	5mg by slow IV injection; repeated every 5min up to maximum of 15mg 50mg PO bd/tds, up to total daily dose of 300mg
Verapamil	5mg IV over 2min; repeated after 5min 40–120mg PO tds

Algorithm for management of tachyarrhythmias

Fig. 18.6 shows the management algorithm for broad and narrow complex tachycardias.

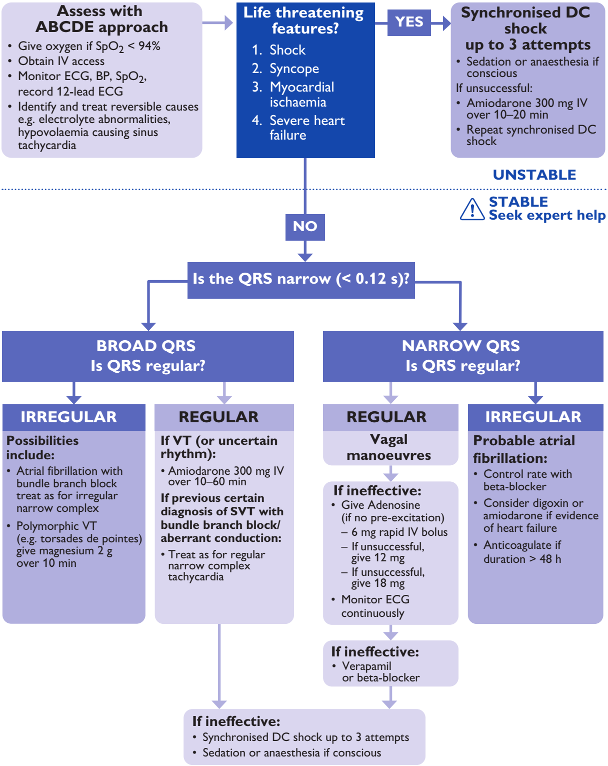
Assess with ABCDE approach
• Give oxygen if SpO_2 < 94%
• Obtain IV access
• Monitor ECG, BP, SpO_2, record 12-lead ECG
• Identify and treat reversible causes e.g. electrolyte abnormalities, hypovolaemia causing sinus tachycardia
Life threatening features?
1. Shock
2. Syncope
3. Myocardial ischaemia
4. Severe heart failure
YES
Synchronised DC shock up to 3 attempts
• Sedation or anaesthesia if conscious
If unsuccessful:
• Amiodarone 300 mg IV over 10–20 min
• Repeat synchronised DC shock
UNSTABLE
STABLE
Seek expert help
NO
Is the QRS narrow (< 0.12 s)?
BROAD QRS
Is QRS regular?
NARROW QRS
Is QRS regular?
IRREGULAR
Possibilities include:
• Atrial fibrillation with bundle branch block treat as for irregular narrow complex
• Polymorphic VT (e.g. torsades de pointes) give magnesium 2 g over 10 min
REGULAR
If VT (or uncertain rhythm):
• Amiodarone 300 mg IV over 10–60 min
If previous certain diagnosis of SVT with bundle branch block/ aberrant conduction:
• Treat as for regular narrow complex tachycardia
REGULAR
Vagal manoeuvres
If ineffective:
• Give Adenosine (if no pre-excitation)
– 6 mg rapid IV bolus
– If unsuccessful, give 12 mg
– If unsuccessful, give 18 mg
• Monitor ECG continuously
If ineffective:
• Verapamil or beta-blocker
IRREGULAR
Probable atrial fibrillation:
• Control rate with beta-blocker
• Consider digoxin or amiodarone if evidence of heart failure
• Anticoagulate if duration > 48 h
If ineffective:
• Synchronised DC shock up to 3 attempts
• Sedation or anaesthesia if conscious

Fig. 18.6 Management of broad and narrow complex tachycardias. For further information, see The Resuscitation Council (UK) website (☞ http://www.resus.org.uk/).

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Bradyarrhythmias

Definition

- HR <60bpm.

Management

- Assessment of airway, breathing, and circulation.
- Oxygen should be administered to hypoxic patients.
- IV access should be gained and bloods taken, including clotting, Hb, U&Es, LFTs, glucose, CRP, troponin, glucose, K^+, Mg^{2+}, and Ca^{2+}.
- An ABG/VBG may be also useful for rapid assessment of acid–base status.
- A 12-lead ECG should be obtained, where possible, to further assist in identification of the underlying rhythm.
- Unstable patients are those in shock or who have had syncope, myocardial ischaemia, and HF.
- Give atropine 500mcg IV and repeat, if required, every 3–5min to a total of 3mg.
- If the patient remains unstable, consider cardiac pacing or isoprenaline infusion.
- In some cases, alternative pharmacotherapy should be considered prior to pacing (e.g. IV glucagon if a β-blocker or CCB is a likely cause of the bradycardia).

Pacing

See ➔ Permanent pacemaker: overview, p. 674 for further information on methods of pacing.

Transcutaneous pacing

- If no response to atropine, commence isoprenaline (5mcg/min IV) or commence transcutaneous pacing.
- Monitor for electrical capture and check for simultaneous pulse.
- Use sedation and analgesia as required.

Percussion pacing

- If no response to atropine and transcutaneous pacing is not available, percussion pacing can be attempted.
- Form a closed fist and give repeated thumps over the left lower edge of the sternum at a rate of 50–70bpm.

Transvenous pacing

- Temporary transvenous pacing should be considered if there is documented recent asystole, ventricular pause of >3s, Mobitz type II AV block or CHB (especially broad QRS or HR <40bpm).

Algorithm for management of bradyarrhythmias

Fig. 18.7 shows the management algorithm for bradyarrhythmias.

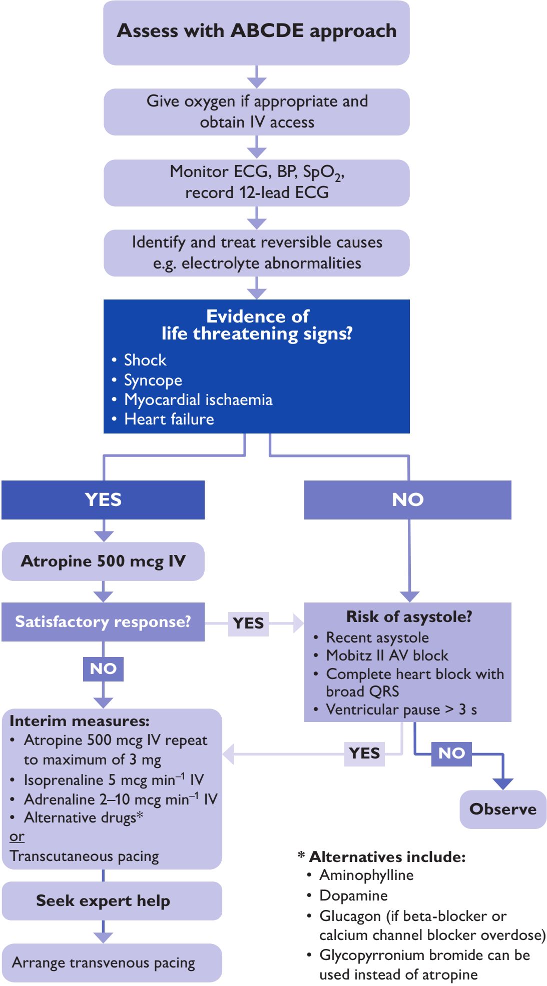
Assess with ABCDE approach
Give oxygen if appropriate and obtain IV access
Monitor ECG, BP, SpO2, record 12-lead ECG
Identify and treat reversible causes e.g. electrolyte abnormalities
Evidence of life threatening signs?
• Shock
• Syncope
• Myocardial ischaemia
• Heart failure
YES
NO
Atropine 500 mcg IV
Satisfactory response?
YES
Risk of asystole?
• Recent asystole
• Mobitz II AV block
• Complete heart block with broad QRS
• Ventricular pause > 3 s
NO
Interim measures:
• Atropine 500 mcg IV repeat to maximum of 3 mg
• Isoprenaline 5 mcg min⁻¹ IV
• Adrenaline 2–10 mcg min⁻¹ IV
• Alternative drugs*
or
Transcutaneous pacing
YES
NO
Observe
Seek expert help
Arrange transvenous pacing
* Alternatives include:
• Aminophylline
• Dopamine
• Glucagon (if beta-blocker or calcium channel blocker overdose)
• Glycopyrronium bromide can be used instead of atropine

Fig. 18.7 Management of bradyarrhythmias. For further information, see The Resuscitation Council (UK) website (http://www.resus.org.uk/).

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Malignant hypertension

See ➲ Malignant hypertension, pp. 40–1 for further information.

Definition

- Diagnosed on the basis of ≥ grade III hypertension (≥180/100mmHg) associated with new or worsening target organ dysfunction.

Clinical features

- Patients may present with headache, visual disturbances, chest pain, and shortness of breath.
- Patients with hypertensive encephalopathy may present with tonic–clonic seizures and loss of consciousness/confusion.

Investigations

- *Bloods:* FBC, blood film, U&Es, troponin, NT-proBNP.
- *Urine*: haematuria/proteinuria; consider toxicology.
- *ECG:* assessment of ongoing ischaemia/infarction, LVH.
- *CXR:* assessment of pulmonary oedema.
- *Echocardiography:* assessment of LV function.
- *Fundoscopy:* assessment of hypertensive changes (see ➲ Box 1.5).
- *CT/MRI:* if neurological symptoms present.

Management

- The aim of management is to reduce mean arterial pressure (MAP) by 25%.
- *Labetalol:* should be administered in 20mg boluses IV every 10min or given as 0.5–2mg/min IV infusion until the intended reduction in BP is achieved. The maximum dose should not exceed 300mg.
- *Sodium nitroprusside:* second-line agent, administer as an infusion of 0.3–0.5mcg/kg/min, ↑ by 0.5mcg/kg/min every 5min until goal BP is achieved. The maximum dose should not exceed 10mcg/kg/min.

Pulmonary embolism

Epidemiology

- VTE, including PE and DVT, is the third most common CV syndrome, after ACS and CVA, occurring in 39–115 per 100,000.

Predisposing factors for pulmonary embolism

Strong risk factors

- Lower limb fracture
- Hip or knee replacement
- Major trauma
- Spinal cord injury
- MI (<3 months)
- Hospitalization for AF/HF (<3 months)

Moderate risk factors

- Oral contraceptive pill (OCP)/HRT
- Post-partum
- Cancer
- Chemotherapy
- Stroke (paralytic)
- Infection
- Autoimmune
- Thrombophilia
- Central venous lines

NB prolonged sitting, obesity, pregnancy, and bed rest for >3 days may also ↑ the risk of PE, but to a lesser degree than the above-listed strong and moderate risk factors.

Clinical features

Symptoms

- Chest pain
- Shortness of breath
- Syncope
- Haemoptysis

Signs

- Tachycardia
- Tachypnoea
- Hypotension
- Raised JVP with prominent ‘a’ waves
- Parasternal heave
- On auscultation: S3/TR/wide splitting of S2/PR

Investigations

- *Bloods:* FBC, clotting, U&Es, troponin, NT-proBNP, D-dimer.
- *ABG:* normal ABG *does not* exclude PE. ↓ PaO2 with larger PEs. Other changes include mild respiratory alkalosis and ↓ PaCO2 (due to tachypnoea) and metabolic acidosis (secondary to shock).
- *ECG:* commonly shows sinus tachycardia ± non-specific ST-segment and T wave changes in anterior chest leads. Features of RV strain such as TWI in leads V1–V4, $S_1Q_3T_3$; complete or incomplete RBBB is usually seen with large PEs. Patient may have AF.
- *CXR:* may be normal. A near-normal CXR with severe respiratory compromise is suggestive of PE. Less commonly, may show focal pulmonary oligaemia (*Westermark’s sign*), raised hemidiaphragm,

small pleural effusion, wedge-shaped shadows based on the pleura, subsegmental atelectasis, or dilated proximal pulmonary arteries.
- *Echocardiography:* may show RV dilatation, flattened IVS, distended IVC with ↓ collapsibility, pulmonary acceleration time <60ms, mildly elevated (<60mmHg) TV gradient, ↓ TAPSE, ↓ S′ at the TV annulus, global hypokinesia (with apical sparing—*McConnell's sign*), PA dilatation, and TR/PR. Rarely, thrombus in the PA may be visible.
- *CTPA:* in those with low/intermediate probability of PE, a negative CTPA has a high negative predictive value for PE (96%/89%, respectively); however, a negative predictive value of only 60% if the pre-test probability is high. The positive predictive value is high where the pre-test probability of PE is intermediate/high (>90%). Consider other investigations if conflict between clinical suspicion and test result.
- *V/Q scan:* acute PE will show as normal ventilation in a hypoperfused segment (mismatch). Although ↓ radiation vs CTPA and a cheap mode of investigation, V/Q scans are inconclusive in 50% of cases and there is no ability to provide an alternative diagnosis if PE is excluded.
- *US of the lower limb:* the majority of PEs originate from a DVT (70%).

Diagnosis

- If haemodynamic instability, diagnosis can be made with bedside echocardiography or CTPA.
- In those without haemodynamic instability, assess the likelihood of PE.
- The Wells score (see Box 18.2) is used to predict the likelihood of PE.
- If high likelihood, perform CTPA. If intermediate/low likelihood, perform a D-dimer and CTPA only if positive.

Box 18.2 Wells clinical prediction rule (simplified)

High-risk factors (each worth 1 point)

- Previous PE/DVT
- Heart rate >100
- Surgery or immobilization (within last 4 weeks)
- Haemoptysis
- Active cancer
- Clinical signs of DVT
- Alternative diagnosis less likely than PE

PE unlikely if score 0–1; PE likely if score ≥2.

Adapted from Supplementary Table 1 Konstantinides SV *et al. EHJ* 2020: 41; 543–603.

Risk stratification for acute PE

- Pulmonary Embolism Severity Index (PESI) identifies those at ↓ 30-day mortality risk (see Fig. 18.8).
- Simplified PESI index: 30-day mortality risk is 1% if NONE of the following risk factors is present: age >80 years; cancer; chronic pulmonary disease; HR >110bpm; SBP >100mmHg; and arterial saturations <90%. If one or more risk factors are present, 30-day mortality risk is 10.9%.

High-risk pulmonary embolism

- Cardiac arrest.
- SBP <90mmHg and evidence of end-organ hypoperfusion.
- SBP <90mmHg or drop of >40mmHg for >15min not attributable to another cause.

Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/ or comorbidity: PESI class III–V or sPESI ≥1	RV dysfunction on TTE or CTPA	Elevated cardiac troponin levels[b]
High		+	(+)	+	(+)
Intermediate	Intermediate–high	-	+	+	+
	Intermediate–low	-	+	One (or none) positive	
Low		-	-	-	Assesment optional; if assessed, negative

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BP = blood pressure; CTPA = computed tomography pulmonary angiography; H-FABP = heart-type fatty acid-binding protein; NT-proBNP = N-terminal pro B-type natriuretic peptide; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; sPESI = simplified Pulmonary Embolism Severity Index; TTE = trans-thoracic echocardiogram.

[a] Cardiac arrest, obstructive shock, persistent hypotension.

[b] Biomarkers include troponon, NT-proBNP, and H-FABP.

Fig. 18.8 Classification of pulmonary embolism severity and the risk of early in-hospital or 30-day death. .

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Management of acute PE

Management of high-risk pulmonary embolism

- Assessment of airway, breathing, and circulation.
- Management of all-risk PEs is shown in Fig. 18.9.

Airway and oxygenation

- Oxygen should be administered to patients with SaO_2 <90%.
- NIV, CPAP, and BiPAP should be considered. However, as positive intrathoracic pressure can ↓ venous return, positive end-expiratory pressure should be carefully employed.
- Intubation may be required if non-invasive strategies fail. However, as those with RV failure are hypotensive/high risk for hypotension during anaesthetic induction, only perform if unable to tolerate NIV.

Right ventricular failure

- If CVP is ↓, consider cautious volume loading with 500mL boluses of 0.9% sodium chloride over 15–30min. Care must be taken not to overdistend the RV and lead to ↓ CO.
- Inotropes (e.g. dobutamine 2–20mcg/kg/min) ↑ RV inotropy and lower filling pressures.
- Vasopressors (e.g. noradrenaline 0.2–1.0mcg/kg/min) ↑ RV inotropy and BP. However, excess vasoconstriction ↓ tissue perfusion.
- Dobutamine may worsen hypotension if used without a vasopressor and may also have a pro-arrhythmogenic effect.
- ECMO or ECLS may be required for short-term support (see ➔ Mechanical circulatory support, pp. 116–18 for further information).

Initial anticoagulation

- In patients with intermediate/high probability of PE, anticoagulation should be initiated with LMWH or UFH (if overt haemodynamic instability/severe renal impairment) whilst waiting for diagnostic tests.

Thrombolysis

- Thrombolysis should be considered in high-risk PE (see Fig. 18.8).
- Greatest benefit if a patient is thrombolysed within 48h but can be used up to 6–14 days from symptom onset.
- *Recombinant tissue plasminogen activator (rtPA):* given at a dose of 100mg over 2h (or an accelerated regime of 0.6mg/kg over 15min (max. dose 50mg)).
- *Streptokinase:* given as a 250,000IU loading dose over 30min, followed by 100,000IU/h over 12–24h (or an accelerated regime of 1.5 million IU over 2h).
- *Urokinase:* given as a 4400IU/kg loading dose over 10min, followed by 4400IU/kg/h over 12–24h (or an accelerated regime of 3 million IU over 2h).
- *Percutaneous catheter-guided thrombolysis:* should be considered in patients where thrombolysis has failed or is contraindicated (see Box 18.3), or as an alternative to surgical embolectomy if this is not available.

Surgical pulmonary embolectomy

- This is recommended in those with high-risk acute PE where thrombolysis has failed or is contraindicated.

Box 18.3 Contraindications to thrombolysis

Absolute

- Previous intracranial haemorrhage
- Cerebrovascular accident (<6 months)
- Central nervous system tumours/arteriovenous malformations
- Recent major trauma/head injury/surgery (<1 month)
- Bleeding diathesis
- Active bleeding

Relative

- Transient ischaemic attack (<6 months)
- Oral anticoagulation
- Pregnancy/first week post-partum
- Non-compressible puncture (e.g. liver biopsy, lumbar puncture) (<24h)
- Traumatic resuscitation
- Refractory hypertension (SBP >180mmHg)
- Advanced liver disease
- Active peptic ulcer

Oral anticoagulation

- Once the patient is stabilized, they should be commenced on oral anticoagulation. A DOAC is preferred to a VKA in this setting.
- Duration of anticoagulation should be determined in a dedicated VTE clinic as an outpatient.

Cardiac arrest

- Massive PE may present as cardiac arrest with electromechanical dissociation (EMD).
- Chest compressions may help to break up the thrombus and allow it to progress more distally, thereby restoring some CO.
- If clinical suspicion of PE is high and there is no absolute contraindication to thrombolysis, give rtPA.
- Continue CPR for at least 60–90min.

Management of low/intermediate-risk pulmonary embolism

Distinguishing low from intermediate risk

1. Clinical features of severity or serious comorbidity: simplified PESI (sPESI) score ≥1.
2. Presence of RV dysfunction.

Intermediate risk

- If '1' or '2' above is present, troponin should be measured.
- If troponin positive plus RV dysfunction: intermediate to high risk.
- If troponin negative: intermediate to low risk.

Low risk

- If neither '1' nor '2' above is present.

Algorithm for acute PE treatment

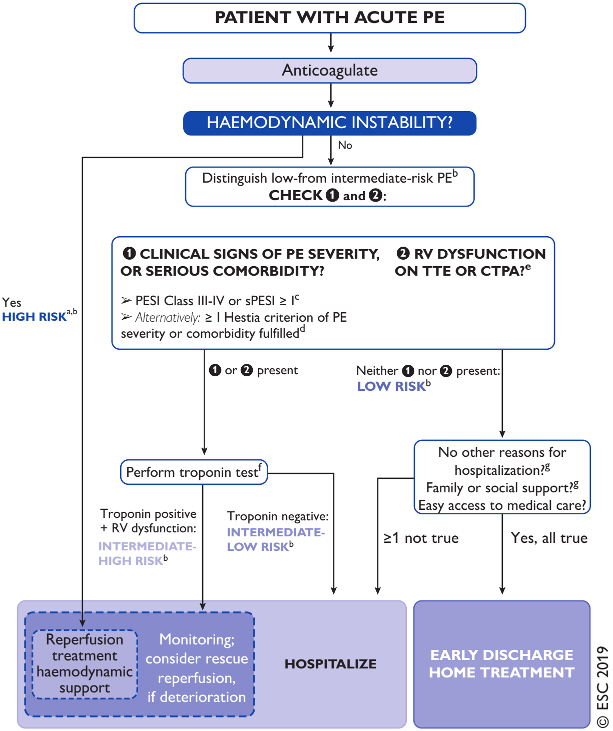
PATIENT WITH ACUTE PE
Anticoagulate
HAEMODYNAMIC INSTABILITY?
No
Distinguish low-from intermediate-risk PE[b]
CHECK ❶ and ❷:
Yes
HIGH RISK[a,b]
❶ CLINICAL SIGNS OF PE SEVERITY, OR SERIOUS COMORBIDITY?
➢ PESI Class III-IV or sPESI ≥ I[c]
➢ *Alternatively:* ≥ I Hestia criterion of PE severity or comorbidity fulfilled[d]
❷ RV DYSFUNCTION ON TTE OR CTPA?[e]
❶ or ❷ present
Neither ❶ nor ❷ present:
LOW RISK[b]
Perform troponin test[f]
Troponin positive + RV dysfunction:
INTERMEDIATE-HIGH RISK[b]
Troponin negative:
INTERMEDIATE-LOW RISK[b]
No other reasons for hospitalization?[g]
Family or social support?[g]
Easy access to medical care?
≥1 not true
Yes, all true
Reperfusion treatment haemodynamic support
Monitoring; consider rescue reperfusion, if deterioration
HOSPITALIZE
EARLY DISCHARGE HOME TREATMENT
© ESC 2019

Fig. 18.9 Management of acute pulmonary embolism.

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Aortic dissection

Epidemiology

- Estimated incidence 6/100,000 persons/year; ↑ in men, ↑ with ↑ age.

Aetiology

- Risk factors include ↑ BP, smoking, trauma, pre-existing aortic pathology (known AV disease, thoracic aneurysm, previous aortic surgery, Marfan syndrome), and family history (aortic disease).

Basic pathology

- This is caused by disruption of the medial layer of the aortic wall, resulting in the formation of a true lumen and a false lumen.
- There may be an initial intimal tear and tracking of blood within the media and either an aortic rupture or a second intimal tear.
- A dissection can either be retrograde or anterograde.

Classification

- There are three classifications, as illustrated in Fig. 18.10.

Clinical features

Symptoms

- Most common; acute-onset chest pain (type A), abdominal/back pain (type B).
- Patients may experience pain following the dissection path.
- Other features include syncope and neurological symptoms (secondary to hypoperfusion, thromboembolism, or peripheral nerve compression).

Signs

- High-risk signs include pulse deficit, SBP difference, new aortic diastolic murmur, focal neurology, and hypotension/shock.

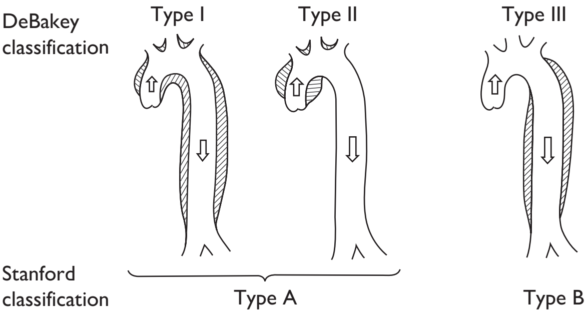


Fig. 18.10 Classification of aortic dissection.

Complications

- AR (may lead to HF).
- Cardiac tamponade.
- Aortic rupture.
- Myocardial ischaemia (compression/obliteration of the coronary ostia, continuation of the dissection into the coronary tree).
- Mesenteric ischaemia.
- Renal failure (secondary to hypoperfusion or infarction).
- CVA.

Investigations

- *Bloods:* FBC, clotting, U&Es, LFTs, CRP, troponin, NT-proBNP, D-dimer (if the D-dimer is raised acutely, this raises the suspicion of aortic dissection); crossmatch at least 10 units.
- *ABG:* to assess metabolic state.
- *ECG:* to assess for ischaemia and arrhythmias.
- *Echocardiography:* may detect intimal flaps, AR, and cardiac tamponade. The sensitivity and specificity of TTE for evaluation of aortic dissection in the ascending aorta is 77–80% and 93–96%, respectively. The equivalent values for TOE are 99% and 89%, respectively.
- *CT:* the key finding is the presence of a flap separating two lumens; this has a sensitivity of >95%.
- *MRI:* this has the highest sensitivity and specificity for diagnosing aortic dissection (98%).

CT, MRI, and TOE are considered equivalent for diagnosis. CT and MRI are superior in assessing extension and branches involved. CT is the most commonly used imaging modality for diagnosis in the acute setting. Given the length of time involved for each scan, MRI is rarely used for acute diagnosis.

Diagnosis

- Diagnosis is based on risk stratification based on the number of groups (high-risk conditions/high pain features/high-risk examination features) involved—0, 1, 2, or 3 (see Table 18.4). Low probability of aortic dissection: a score of 0–1 high-risk features; and high probability: a score of 2–3 high-risk features.

The flow chart in Fig. 18.11 illustrates the decision-making process.

Table 18.4 High-risk features

Conditions	Pain	Examination
• Marfan syndrome • Thoracic aortic aneurysm • Previous aortic pathology • Known AV disease • Family history of aortic pathology	• Chest/back/abdominal pain • Abrupt onset • Severe • Ripping/tearing	• Pulse deficit • Focal neurology • SBP difference • New AR • Hypotension/shock

AV, arteriovenous; SBP, systolic blood pressure; AR, aortic regurgitation.

Management of acute aortic dissection

Stabilizing the patient

- Assessment of airway, breathing, and circulation.
- Secure *venous access* with large-bore cannulae.
- When the diagnosis is confirmed or in cases with CV complications, *transfer to ICU* and insert an *arterial line* (radial unless the subclavian artery is compromised when a femoral line is preferred), a *central venous line*, and a *urinary catheter*.
- Immediate measures should be taken to correct BP (see ➔ Blood pressure control below).
- Give adequate analgesia (diamorphine 2.5–10mg IV and metoclopramide 10mg IV).
- In all but those patients who are hypotensive, initial management is aimed at reducing BP and myocardial contractility. The goal is to stop spread of the intramural haematoma and prevent rupture. The best guide is control of pain.
- Strict bed rest in a quiet room is essential.

Blood pressure control

Hypertension

- Reduce SBP to 100–120mmHg.
- Start on IV labetalol (if no contraindications), aiming to reduce HR to 60–70bpm (see Box 18.4).
- Further antihypertensive therapy may be necessary.
- In patients with AR and CCF, myocardial depressants should not be given. Control BP with vasodilators only.

Hypotension

- May be due to haemorrhage or cardiac tamponade.
- Resuscitate with rapid IV volume.
- If there are signs of AR or cardiac tamponade, arrange for urgent echocardiography and discuss with the surgeons.

Box 18.4 Medical therapy of aortic dissection

β-blockade (aim for heart rate <60–70bpm)

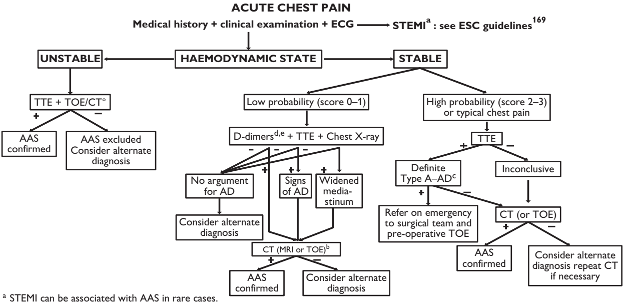
Labetalol	20–80mg slow IV injection over 10min, then 20–200mg/h IV, increasing every 15min 100–400mg PO every 12h

When heart rate 60–70bpm (or if β-blocker contraindicated), add

Nitroprusside	0.25–10mcg/kg/min IV infusion
Hydralazine	5–10mg IV over 20min 50–300mcg/min IV infusion 25–50mg PO every 8h
Glyceryl trinitrate	1–10mg/h IV infusion
Amlodipine	5–10mg PO od

Medical vs surgical management

- Surgery is the treatment of choice for type A dissection. Surgery reduces 1-month mortality from 90% to 30%.
- This is usually performed, as long as the aortic valve is normal, with aortic valve-sparing repair of the aortic root.
- Patients with uncomplicated type B dissection should be stabilized with pain and BP control.
- Patients with complicated type B dissection should undergo thoracic endovascular repair (TEVAR). If this is not anatomically feasible, surgery is required to replace the descending aorta with a Dacron graft.


ACUTE CHEST PAIN
Medical history + clinical examination + ECG
STEMI[a] : see ESC guidelines[169]
UNSTABLE
HAEMODYNAMIC STATE
STABLE
TTE + TOE/CT[b]
+
–
AAS confirmed
AAS excluded Consider alternate diagnosis
Low probability (score 0–1)
D-dimers[d,e] + TTE + Chest X-ray
–
–
–
+
+
+
No argument for AD
Signs of AD
Widened media-stinum
Consider alternate diagnosis
CT (MRI or TOE)[b]
+
–
AAS confirmed
Consider alternate diagnosis
High probability (score 2–3) or typical chest pain
TTE
+
–
Definite Type A–AD[c]
Inconclusive
+
–
Refer on emergency to surgical team and pre-operative TOE
CT (or TOE)
+
–
AAS confirmed
Consider alternate diagnosis repeat CT if necessary

[a] STEMI can be associated with AAS in rare cases.
[b] Pending local availability, patient characteristics, and physician experience.
[c] Proof of type-A AD by the presence of flap, aortic regurgitation, and/or pericardial effusion.
[d] Preferably point-of-care, otherwise classical.
[e] Also troponin to detect non–ST-segment elevation myocardial infarction.

Fig. 18.11 Algorithm for the diagnosis of aortic dissection.

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Cardiac tamponade

Aetiology

See ➔ Common causes of cardiac tamponade, p. 298 for further information on epidemiology and aetiology.

Basic pathology

- The primary defect in cardiac tamponade is interference with diastolic filling of the heart.

Clinical features

Symptoms

- Chest pain may be typically pericardial or may be dull and heavy due to distension of the pericardium.
- Dyspnoea is common.
- Orthopnoea may occur later in the course of the disease. Cough may be present due to compression of surrounding structures.
- Constitutional symptoms may be present, depending on the cause of the disease.

Signs

- Hypotension, raised JVP, and quiet heart sounds (Beck's triad).
- Tachycardia.
- Pulsus paradoxus (fall in SBP on inspiration of >10mmHg or inspiratory fall in SBP that exceeds half of the pulse pressure).
- Elevated JVP with brisk 'x' descents and absent 'y' descents, and rise in JVP on inspiration (Kussmaul's sign).
- Dyspnoea or tachypnoea with clear lungs.
- Hepatomegaly.

Investigations

- *ECG:* sinus tachycardia, generalized low-voltage QRS complexes with non-specific ST-segment and T wave changes. Electrical alternans, alternating QRS complex amplitude, suggests the presence of a massive pericardial effusion. Total electrical alternans (P–QRS–T), which is uncommon, is pathognomonic of cardiac tamponade.
- *Echocardiography:* is diagnostic, showing an ECHO-free zone surrounding the heart. The fluid may not be evenly distributed. Diastolic collapse of the RV and RA indicates cardiac tamponade. Variation in TV inflow is also seen in cardiac tamponade (peak E-wave velocity drops by ~40% on inspiration). The IVC is usually dilated, with minimal/no inspiratory collapse.
- *CXR:* shows a large globular heart, usually with clear lung fields.

Management

- Cardiac tamponade is a life-threatening condition—urgent pericardial aspiration is necessary (see ➔ Pericardial aspiration, pp. 716–17 for details on the procedure).
- Surgical drainage is indicated for haemopericardium or purulent pericarditis.

Chapter 19

Sports cardiology

Exercise physiology *862*
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Criteria for interpretation of the athlete's ECG *866*
Further investigations based on ECG abnormalities *868*
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The athlete's heart: right ventricular structural changes *874*
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Causes of sudden cardiac death *878*
Prevention of sudden cardiac death in athletes *880*
Differentiating physiological adaptation from cardiomyopathy *882*
Cardiomyopathies: recommendations for sports participation *884*
Arrhythmias: recommendations for sports participation *886*
Ischaemic heart disease: recommendations for sports participation *888*
Hypertension: recommendations for sports participation *891*
Valvular heart disease: recommendations for sports participation *892*

Exercise physiology

- At the onset of exercise, HR and SV ↑ in order to ↑ CO. This is accompanied by changes in arterial BP and peripheral vascular resistance. These changes are controlled by the autonomic nervous system.
- The ability of the CV system to supply muscles with oxygen during exercise is measured by VO_2 max. This is the point at which there is a plateau in oxygen uptake despite an ↑ in workload.

Increase in cardiac output

- HR ↑ as a direct result of withdrawal of the parasympathetic drive in favour of sympathetic stimulation. This also leads to ↑ contractility.
- Although SV ↑ secondary to ↑ contractility, it is influenced more markedly by venous return in the early stages of exercise. ↑ venous return causes an ↑ in LV end-diastolic volume (LVEDV); this, in turn, causes the myocardium to stretch, leading to a stronger contraction (Frank–Starling mechanism).
- A normal SV is 50–60mL/beat, and 70–90mL/beat in an athlete.
- CO is a product of HR and SV. The usual CO is between 5L/min which can ↑ to up to 25–30L/min in an athlete.

Changes in peripheral vasculature

- In muscle, some capillaries have minimal blood flow at rest. During exercise, these capillaries vasodilate, improving blood flow to the muscles necessary for oxygen delivery and is triggered by oxygen depletion. This is controlled by vasoactive compounds.
- Noradrenaline release from vasoconstrictor nerves, stimulated by sympathetic activation, and the release of adrenaline and noradrenaline from the adrenal medulla lead to peripheral vasoconstriction (sparing active muscles). This ↑ blood flow by 2L/min.
- The most profound vasoconstrictor effect is in the venous system, which contains two-thirds of the total blood volume. The effect ↑ the systemic venous filling pressure and return of blood to the heart.

Changes in blood pressure

- During exercise, the SBP ↑, but the DBP remains relatively stable and does not tend to ↑ by >10mmHg. The net effect is ↑ MAP.
- In order to sustain blood supply, the blood flow rate ↑; this is supported by ↑ SBP, which also stretches the vessel walls and further ↑ blood flow.

Changes in respiration

- Oxygen delivery and carbon dioxide removal are facilitated by an ↑ in the rate and depth of respiration.
- Lactic acid generated is initially buffered by bicarbonate and leads to an ↑ in carbon dioxide. This, in turn, stimulates carotid body chemoreceptors, which signal to the respiratory centre in the medulla and ↑ RR.
- Once the buffering capacity is exceeded, the pH falls. This acts as a further signal to drive hyperventilation.
- The ↑ in CO and ventilation, together with alterations in afterload, enables the body to meet the necessary metabolic requirements.

Benefits of exercise

- Exercise leads to a reduction in weight and BP, and improves lipid profiles. It reduces the risk of developing conditions such as diabetes and CVA, and exercising individuals demonstrate a 30–50% reduction in the risk of developing CAD.
- The benefits of exercise are well established.
- Exercise has also been shown to improve overall well-being, preventing conditions such as cancer, osteoporosis, depression, and dementia (see Fig. 19.1).

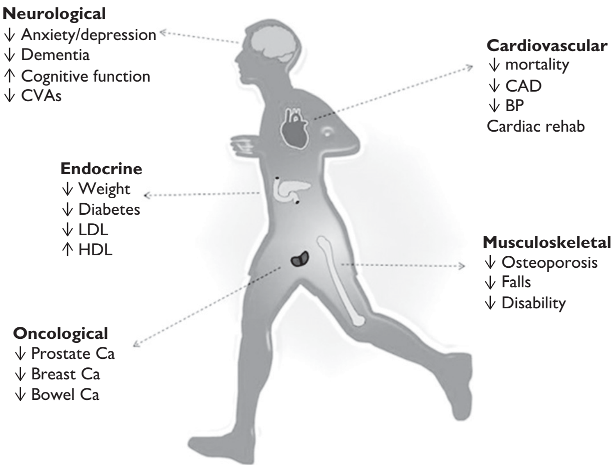
Neurological
↓ Anxiety/depression
↓ Dementia
↑ Cognitive function
↓ CVAs
Cardiovascular
↓ mortality
↓ CAD
↓ BP
Cardiac rehab
Endocrine
↓ Weight
↓ Diabetes
↓ LDL
↑ HDL
Musculoskeletal
↓ Osteoporosis
↓ Falls
↓ Disability
Oncological
↓ Prostate Ca
↓ Breast Ca
↓ Bowel Ca

Fig. 19.1 Benefits of exercise. BP, blood pressure; Ca, cancer; CAD, coronary artery disease; CVA, cerebrovascular accident; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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The athlete's heart: electrical changes

- An athlete is defined as 'one who participates in an organised team or individual sport requiring systematic training and regular competition against others, while placing a high premium on athletic excellence and achievement'.
- The athlete's heart refers to structural and electrical changes that occur in response to intensive exercise. These changes may be evident on a routine ECG, reflecting chamber dilatation, hypertrophy, and ↑ vagal tone.

Normal ECG changes in the athlete's heart

Sinus arrhythmia

- The HR ↑ during inspiration and ↓ during expiration may be exaggerated.[1]

Sinus bradycardia

- In athletes, and in particular endurance athletes, ↑ vagal tone leads to sinus bradycardia. This is defined as HR <60bpm.[1]

Atrial rhythm

- In an atrial rhythm, P waves precede each QRS complex; however, the P waves are of a different morphology to that of sinus P waves. If there are two different P wave morphologies, this is described as a 'wandering atrial pacemaker'.[1]

Junctional rhythm

- This occurs when the rhythm originating in the AVN is faster than that originating from the SAN. This is typically <100bpm and the QRS complex is narrow (<120ms).[1]

First-degree atrioventricular block

- The PR interval is >200ms and each P wave is followed by a QRS complex.[1]

Second-degree atrioventricular block (Mobitz type I/Wenckebach)

- In Mobitz type I, the PR interval ↑ with each beat until the P wave is not conducted. The subsequent PR interval is shorter than the PR interval that preceded the dropped beat.[1]

Isolated incomplete right bundle branch block

- Incomplete RBBB, where there is an RSR pattern with a QRS duration of <120ms, is associated with remodelling of the RV.[1]

Early repolarization

- The J point (the junction between the termination of the QRS complex and the beginning of the ST-segment) is elevated ≥1mV.[1]

Sokolow–Lyon criteria for left ventricular hypertrophy

- Athletes undergo remodelling of their LV, including ↑ in cavity size, as well as in wall thickness. LVH is present when the S wave in lead V1 added to the R wave in leads V5/6 is >35mm.[1]

Anterior T wave inversion

- Up to the age of 16 years, TWI or biphasic T waves may be present from leads V1–V3 due to dominance of the RV. This is known as the 'juvenile pattern'. As the dominance passes from the RV to the LV, there is reversal in TWI, resulting in the adult ECG.
- In adult white athletes, TWI up to lead V2 is acceptable. In black athletes, TWI up to lead V4 is considered an ethnic variant when preceded by coved ST-segment elevation (see Fig. 19.2).[1]

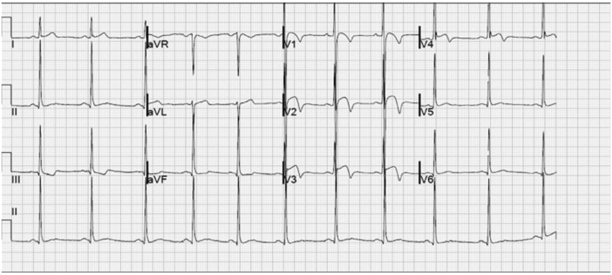

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

Fig. 19.2 Black athlete's ECG.

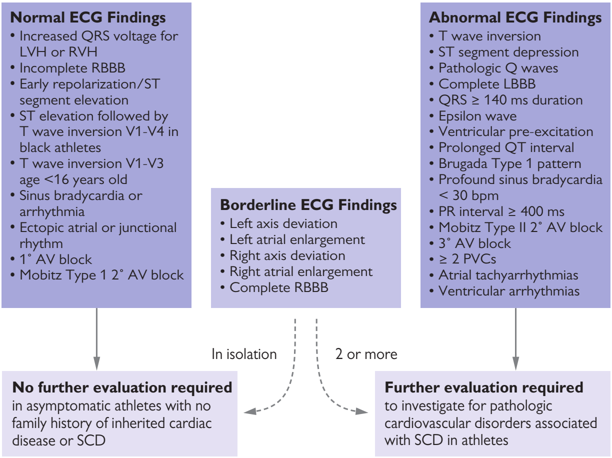
Courtesy of Joyee Basu.

Reference

1. Sharma S, Drezner JA, Baggish A, *et al*. International recommendations for electrocardiographic interpretation in athletes. *J Am Coll Cardiol*. 2017;**69**:1057–75.

Criteria for interpretation of the athlete's ECG

- Some athletes demonstrate ECG changes that overlap with conditions that predispose to SCD. Therefore, it is of vital importance to correctly differentiate physiology from pathology.
- The most up-to-date criteria—international recommendations for ECG interpretation in athletes were published in 2017.[1] These clearly set out the circumstances under which an athlete requires further investigation (see Fig. 19.3).
- Borderline ECG findings (left axis deviation (LAD), RAD, right atrial enlargement (RAE), left atrial enlargement (LAE), and complete RBBB) alone have not been correlated with pathology; however, identification of ≥2 abnormal findings warrant further investigation.



Normal ECG Findings
- Increased QRS voltage for LVH or RVH
- Incomplete RBBB
- Early repolarization/ST segment elevation
- ST elevation followed by T wave inversion V1-V4 in black athletes
- T wave inversion V1-V3 age <16 years old
- Sinus bradycardia or arrhythmia
- Ectopic atrial or junctional rhythm
- 1˚ AV block
- Mobitz Type 1 2˚ AV block

Borderline ECG Findings
- Left axis deviation
- Left atrial enlargement
- Right axis deviation
- Right atrial enlargement
- Complete RBBB

Abnormal ECG Findings
- T wave inversion
- ST segment depression
- Pathologic Q waves
- Complete LBBB
- QRS ≥ 140 ms duration
- Epsilon wave
- Ventricular pre-excitation
- Prolonged QT interval
- Brugada Type 1 pattern
- Profound sinus bradycardia < 30 bpm
- PR interval ≥ 400 ms
- Mobitz Type II 2˚ AV block
- 3˚ AV block
- ≥ 2 PVCs
- Atrial tachyarrhythmias
- Ventricular arrhythmias

No further evaluation required in asymptomatic athletes with no family history of inherited cardiac disease or SCD

Further evaluation required to investigate for pathologic cardiovascular disorders associated with SCD in athletes

Fig. 19.3 Normal, borderline, and abnormal ECG findings in athletes. AV, atrioventricular block; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; PVC, premature ventricular contraction; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; SCD, sudden cardiac death.

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Reference

1. Sharma S, Drezner JA, Baggish A, *et al*. International recommendations for electrocardiographic interpretation in athletes. *J Am Coll Cardiol*. 2017;**69**:1057–75.

Further investigations based on ECG abnormalities

General findings

Pathology	International recommendations[1]
Sinus bradycardia (≤30bpm) Profound first-degree AV block ≥400ms)	Exercise the athlete (running on the spot/climbing stairs) and repeat ECG If no ↑ in HR, exercise stress testing and 24h Holter monitoring
Second-degree (Mobitz type II) and third-degree heart block	Echocardiography, exercise stress testing, 24h Holter monitoring
Pathological Q waves (Q:R ratio of 0.25 or ≥40ms in duration in ≥2 contiguous leads, excluding leads III/aVR)	Repeat ECG if septal Q waves, echocardiography if persistent. If risk factors for coronary artery disease, consider CTCA/functional testing
ST-segment depression (≥0.5mm in ≥2 contiguous leads)	Echocardiography; consider MRI based on clinical suspicion of pathology
Complete LBBB	Echocardiography; if risk factors for coronary artery disease, consider CTCA/functional testing
Non-specific intraventricular delay (≥140ms)	Echocardiography, with additional testing as governed by the results of echocardiography
Epsilon wave (major criterion for ARVC)	Signal-averaged ECG, echocardiography, exercise stress testing, 24h Holter monitoring, MRI
TWI in anterior leads (≥1mm in ≥2 contiguous leads beyond lead V2 in Caucasians and lead V4 in black athletes)	Signal-averaged ECG, echocardiography, exercise stress testing, 24h Holter monitoring, MRI
TWI in lateral/inferolateral leads (≥1mm in ≥2 contiguous inferior/lateral leads, excluding lead III)	Echocardiography, exercise stress testing, 24h Holter monitoring, MRI
TWI in inferior leads (≥1mm in leads II and aVF, excluding lead III)	Echocardiography, exercise stress testing, 24h Holter monitoring. Consider MRI based on clinical suspicion of pathology
LAE (biphasic P wave in lead V1, negative portion ≥40ms in duration and ≥1mm deep), RAE (amplitude >2.5mm in leads II, III, and aVF), LAD ≥−30°, RAD ≥120°, RBBB	Whereas each of these in isolation is not deemed to indicate pathology in the presence of ≥2 or more of these findings, further evaluation should be considered
Low voltages in limb leads	May be associated with ALVC, so should not be ignored in the context of other signs of cardiomyopathy

AV, atrioventricular; HR, heart rate; CTCA, computed tomography coronary angiography; MRI, magnetic resonance imaging; LBBB, left bundle branch block; ARVC, arrhythmogenic right ventricular cardiomyopathy; TWI, T wave inversion; LAE, left atrial enlargement; RAE, right atrial enlargement; LAD, left axis deviation; RAD, right axis deviation; RBBB, right bundle branch block; ALVC, arrhythmogenic left ventricular cardiomyopathy.

ECG diagnosis

Brugada type 1 pattern	Referral to an electrophysiologist
Long QTc (see ➔ Long QT syndrome, pp. 174–6) >470ms in ♂ and >480ms in ♀ athletes	Repeat ECG on a separate occasion. If still prolonged, exercise stress testing and 24h Holter monitoring If QTc is ≥500ms, consider direct referral to an electrophysiologist
Short QT	If ≤320ms, further evaluation is required
Ventricular pre-excitation (see ➔ Atroventricular re-entrant tachycardia, p. 152)	Exercise ECG, echocardiography; consider electrophysiological testing
Atrial arrhythmias	Echocardiography, exercise stress testing, 24h Holter monitoring
Ventricular arrhythmias	Echocardiography, exercise stress testing, 24h Holter monitoring, MRI
Multiple PVEs (≥2 on a resting 12-lead ECG)*	Signal-averaged ECG, echocardiography, exercise stress testing, 24h Holter monitoring, MRI if evidence of >2000 PVEs or NSVT Detraining should be considered if ectopy thought to be caused by myocarditis

* Characteristics of ectopics.

MRI, magnetic resonance imaging; PVE, premature ventricular ectopic; NSVT, non-sustained ventricular tachycardia.

- Infundibular:
  - Left bundle branch block (LBBB) with late precordial transition (where the QRS becomes predominantly positive), R/S = 1 after lead V3, and inferior axis—right ventricular outflow tract (usually benign)
  - LBBB with early precordial transition, R/S = 1 by leads V2/V3 and inferior axis—left ventricular outflow tract (usually benign)
- Fascicular:
  - Right bundle branch block (RBBB) with superior axis and QRS <130ms—left posterior fascicle (usually benign)
  - RBBB with inferior axis and QRS <130ms—right posterior fascicle (usually benign)
- Abnormal:
  - RBBB and QRS ≥130ms—mitral valve, papillary muscles, or left ventricle (may be associated with disease)
  - LBBB with superior axis—septum or right ventricular wall (may be associated with disease)

Reference

1. Sharma S, Drezner JA, Baggish A, *et al*. International recommendations for electrocardiographic interpretation in athletes. *J Am Coll Cardiol*. 2017;**69**:1057–75.

The athlete's heart: left ventricular structural changes

- An athlete's heart commonly undergoes structural changes. The atria and ventricles may enlarge, and the LV wall may thicken. The extent of such changes depends on age, sex, ethnicity, and sporting discipline.
- There is often an overlap between normal athletic adaptation and pathology. The following section gives a general approach to the assessment of, and normal structural findings in, the athletic heart.

Assessment of athlete's left ventricle

- LV remodelling is related to sporting discipline. Power sports (high static component) can lead to ↑ wall thickness and modest ↑ in cavity size. Mixed sports (dynamic and static components) can lead to ↑ cavity size and modest ↑ in wall thickness. Endurance sports (high dynamic component) can lead to ↑ cavity size and wall thickness.
- LV size also differs, based on ethnicity and sex (see Table 19.1).

Table 19.1 Normal left ventricular parameters in ♂ and ♀ athletes

♂	White	Black
LV cavity size (mm)	≤64	≤62
LV wall thickness (mm)	≤12	≤15
♀	White	Black
LV cavity size (mm)	≤57	≤56
LV wall thickness (mm)	≤11	≤12

These values are provided as a guide and do not account for extremes of body size.

Source: data from Dores *et al*. The hearts of competitive athletes: an up to date overview of exercise induced cardiac adaptations. *Revisita Portuguesa de Cardiological*, 2015 and Wilson M *et al*. *IOC Manual of Sports Cardiology* (2016), John Wiley & Sons.

Relative wall thickness

- Relative wall thickness (RWT) is a useful measurement when differentiating between physiology and pathology.
- Calculated by summing the posterior and septal wall thickness in diastole and dividing it by the LV cavity size. This may provide a normal value (<0.42) or demonstrate concentric remodelling (↑ RWT >0.42 and normal mass), concentric hypertrophy (↑ RWT and ↑ mass), and eccentric hypertrophy (normal RWT and ↑ mass) (see Fig. 19.4).

Left ventricular function

- Athletes commonly appear to have a low LVEF, particularly those with an enlarged ventricle, as they are able to generate the required SV with minimal contractility. The diastolic function in an athlete should be normal (E/E′ <12 and E′ >9cm/s).
- Using the RWT, and LV mass and function, an algorithm can be used to help differentiate between physiology and pathology (see Fig. 19.5).

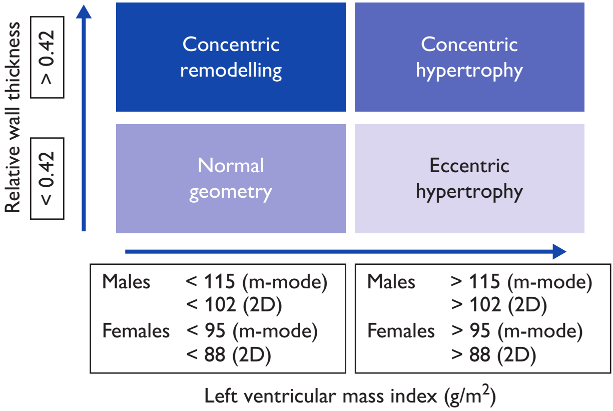
Relative wall thickness
> 0.42
< 0.42
Concentric remodelling
Concentric hypertrophy
Normal geometry
Eccentric hypertrophy
Males < 115 (m-mode) < 102 (2D)
Females < 95 (m-mode) < 88 (2D)
Males > 115 (m-mode) > 102 (2D)
Females > 95 (m-mode) > 88 (2D)
Left ventricular mass index (g/m²)

Fig. 19.4 Left ventricular geometry.

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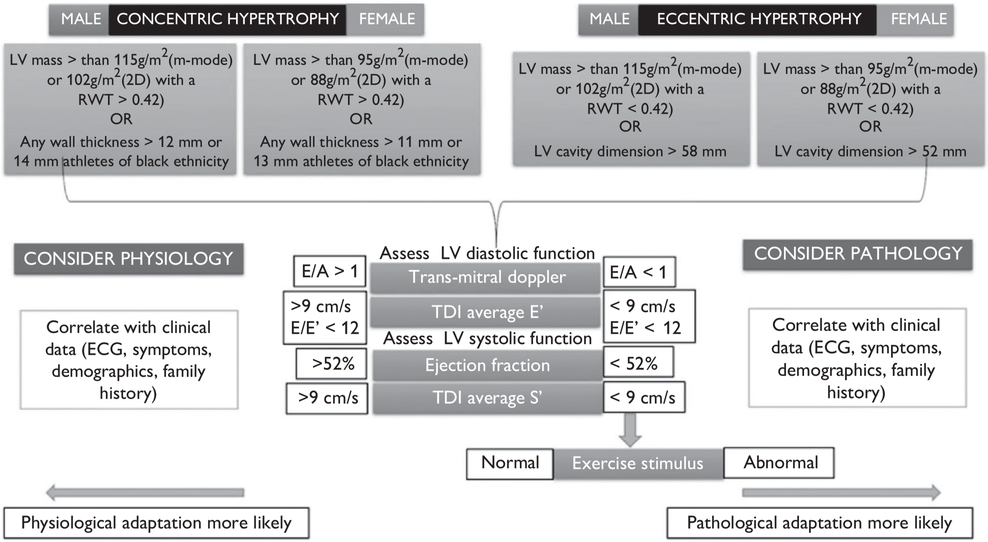
MALE
CONCENTRIC HYPERTROPHY
FEMALE
LV mass > than 115g/m^2(m-mode) or 102g/m^2(2D) with a RWT > 0.42)
OR
Any wall thickness > 12 mm or 14 mm athletes of black ethnicity
LV mass > than 95g/m^2(m-mode) or 88g/m^2(2D) with a RWT > 0.42)
OR
Any wall thickness > 11 mm or 13 mm athletes of black ethnicity
MALE
ECCENTRIC HYPERTROPHY
FEMALE
LV mass > than 115g/m^2(m-mode) or 102g/m^2(2D) with a RWT < 0.42)
OR
LV cavity dimension > 58 mm
LV mass > than 95g/m^2(m-mode) or 88g/m^2(2D) with a RWT < 0.42)
OR
LV cavity dimension > 52 mm
CONSIDER PHYSIOLOGY
Correlate with clinical data (ECG, symptoms, demographics, family history)
Assess LV diastolic function
E/A > 1
Trans-mitral doppler
E/A < 1
>9 cm/s E/E’ < 12
TDI average E’
< 9 cm/s E/E’ < 12
Assess LV systolic function
>52%
Ejection fraction
< 52%
>9 cm/s
TDI average S’
< 9 cm/s
CONSIDER PATHOLOGY
Correlate with clinical data (ECG, symptoms, demographics, family history)
Normal
Exercise stimulus
Abnormal
Physiological adaptation more likely
Pathological adaptation more likely

Fig. 19.5 Differentiating physiological from pathological hypertrophy in an athlete. RWT, relative wall thickness; TDI, tissue Doppler imaging.

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The athlete's heart: right ventricular structural changes

- The RV adapts significantly in dynamic sports.
- The upper limit of RVOT 1 is 44mm, RVOT 2 41mm, RVD 1 49mm, RVD 2 44mm, and RVD 3 92mm (for further information regarding RV size and function assessment, see ➔ Right ventricle, p. 499).
- An algorithm incorporating RV dimensions and function may help to differentiate between pathology and physiology (see Fig. 19.6).

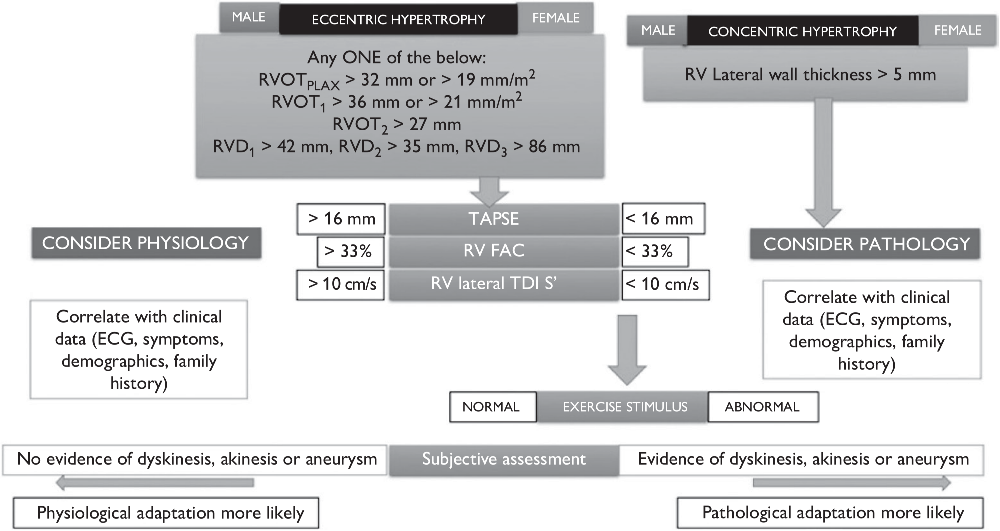
MALE
ECCENTRIC HYPERTROPHY
FEMALE
Any ONE of the below:
$RVOT_{PLAX}$ > 32 mm or > 19 mm/m^2
$RVOT_1$ > 36 mm or > 21 mm/m^2
$RVOT_2$ > 27 mm
RVD_1 > 42 mm, RVD_2 > 35 mm, RVD_3 > 86 mm
MALE
CONCENTRIC HYPERTROPHY
FEMALE
RV Lateral wall thickness > 5 mm
> 16 mm
TAPSE
< 16 mm
> 33%
RV FAC
< 33%
> 10 cm/s
RV lateral TDI S'
< 10 cm/s
CONSIDER PHYSIOLOGY
CONSIDER PATHOLOGY
Correlate with clinical data (ECG, symptoms, demographics, family history)
Correlate with clinical data (ECG, symptoms, demographics, family history)
NORMAL
EXERCISE STIMULUS
ABNORMAL
No evidence of dyskinesis, akinesis or aneurysm
Subjective assessment
Evidence of dyskinesis, akinesis or aneurysm
Physiological adaptation more likely
Pathological adaptation more likely

Fig. 19.6 Differentiating physiological from pathological change in the right ventricle of an athlete. PLAX, parasternal long axis; RV, right ventricle; RVD, right ventricular diameter; RVOT, right ventricular outflow tract; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging.

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Sudden cardiac death in athletes

Epidemiology

- SCD is defined as a 'non-traumatic, unexpected fatal event occurring within 1 hour of the onset of symptoms in an apparently healthy subject. If the death was not witnessed the definition applies when the victim was in good health 24 hours before the event'.
- SCD is the leading cause of death in athletes. A large proportion are associated with undiagnosed CVD. The generally accepted prevalence is 1 in 50,000 in university-aged athletes.
- Athletes have a 2.5-fold ↑ risk of SCD vs sedentary individuals. Sporting activity may be a trigger for life-threatening arrhythmias in those with an underlying cardiac condition.
- The prevalence of underlying cardiac conditions capable of causing SCD in athletes is estimated to be 1 in 300.
- Men are at ↑ risk of SCD. Black athletes and, in particular those playing sports, such as football and basketball, are also at ↑ risk.

Aetiology

The cause of SCD varies by age:

- *<35 years old:* cardiomyopathies and channelopathies predominate.
- *>35 years old:* CAD predominates.
- The leading cause of death in athletes is sudden arrhythmic death syndrome (SADS). Fig. 19.7 illustrates the most common causes of SCD in athletes.

Investigations after sudden cardiac death

- *Autopsy:* should be requested in individuals with suspected SCD in order to determine the cause of death.
- *Heart:* should be examined histologically in a specialist centre and labelled blocks of the myocardium taken from both ventricles.
- *Blood/bodily fluids:* analysed for molecular pathology/toxicology.
- *Spleen:* retained for genetic analysis of potential pathological genes.
- *Screening:* all living first-degree relatives should be referred to a cardiologist with a specialist interest in inherited cardiac conditions for further investigations.

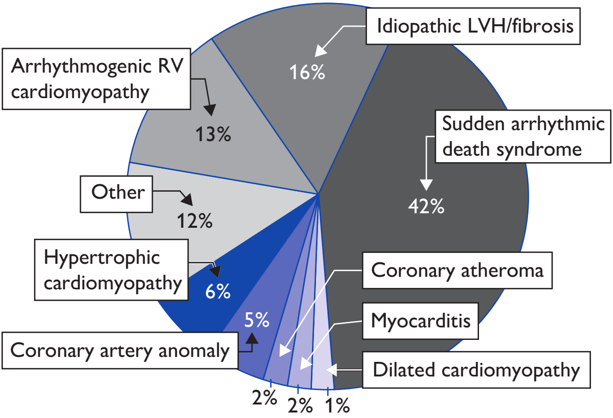

Fig. 19.7 Causes of sudden cardiac death.

Reproduced from Finocchiaro G *et al*. *J Am Coll Cardiol* 2016; **67**(18):2108–15 with permission from Elsevier.

Causes of sudden cardiac death

Coronary artery disorders

Concealed ischaemic heart disease

- This accounts for the majority of SCDs in those aged >35 years, most likely secondary to stress-related plaque rupture and thrombosis formation.
- In the young (aged 14–35 years), IHD occurs secondary to accelerated atherosclerosis. SCD is usually due to myocardial ischaemia secondary to obstructed blood flow, which triggers fatal arrhythmias.

Risk factors

- In older patients: family history, hypercholesterolaemia, diabetes, hypertension, smoking, and high BMI.
- In young patients: dyslipidaemic family history, cocaine/steroid use.

Anomalous coronary arteries

- Blood flow is impeded at the anomalous artery ostium, by compression between the pulmonary trunk and the aorta or by coronary vasospasm.
- Ischaemia may develop during exercise, causing fatal arrhythmias.
- Usually due to an anomalous left coronary artery system originating from the right coronary sinus.

Coronary artery dissection

- Dissection leads to the formation of an intramural haematoma which externally compresses the vessel, leading to myocardial ischaemia.

Cardiomyopathy

Hypertrophic cardiomyopathy

- HCM is characterized by asymmetric ventricular hypertrophy (≥15mm) in the absence of other abnormal loading conditions. Histologically, there is evidence of fibrosis and myocardial disarray.
- Deaths commonly occur in start–stop sports (e.g. basketball/football).
- Death may be secondary to arrhythmia or LVOTO.
- The risk of SCD is generally calculated by using the HCM Risk-SCD score. However, this score is not applicable to an athletic population.

Arrhythmogenic cardiomyopathy

- ACM is characterized by fibrofatty replacement of the myocardium.
- Leads to ventricular wall abnormalities, dilatation, and arrhythmias.
- Although this typically affects the RV, the LV can be affected simultaneously or in isolation.
- The risk of SCD is highest in those who have ventricular tachycardia, syncope, and aborted cardiac arrest.

Dilated cardiomyopathy

- Predisposes to ventricular arrhythmias, bradyarrhythmias, and HF.
- Risk is ↑ in those who are symptomatic and who have LVEF <40%, extensive LGE on MRI, unexplained syncope, or ventricular arrhythmias.
- ↑ risk of malignant ventricular arrhythmias in those with a lamin A/C mutation and ≥2 of risk factors: NSVT on ambulatory monitoring, LVEF ≤45%, ♂ sex, and non-missense mutations.

Myocarditis

- Myocardial inflammation is commonly caused by viral infection. Can present with a viral prodrome and lead to arrhythmias/HF.
- SCD may occur in the active phase (<2 weeks) or later due to arrhythmias. The risk of SCD is ↑ in those with ↓ LVEF and arrhythmias on exercise testing or ambulatory monitoring. Residual LGE on MRI indicative of fibrosis may ↑ risk.

Valvular heart disease

- MVP may lead to SCD in athletes.

Aortic dissection

- Usually occurs in those with a genetic or congenital predisposition at times of intense physical exertion due to a rapid ↑ in BP.
- There may be familial thoracic aortic disease, bicuspid aortic valve, Marfan syndrome, Ehlers–Danlos syndrome, or Loeys–Dietz syndrome.

Channelopathies and arrhythmic conditions

Long QT syndrome

- In athletes, defined as QTc >470ms in men and >480ms in women.
- The risk of SCD is ↑ in those with syncope, aborted cardiac arrest, women with LQT type 2 and QTc >500ms, QTc >500ms with electrical instability, and those with high-risk genetics (two mutations in one individual).

Brugada syndrome

- The risk of SCD is ↑ in those with an aborted cardiac arrest, documented VT, or a spontaneous type I pattern with previous syncope.

Wolff–Parkinson–White syndrome

- Characterized by a short PR interval, delta wave, and widened QRS complex (pre-excitation) on the ECG and arrhythmia/palpitations.
- SCD usually due to 1:1 conduction of AF through an accessory pathway, causing VF. The heart is generally morphologically normal.

Catecholaminergic polymorphic ventricular tachycardia

- Typically occurs during periods of exercise or emotional stress.
- Risk of SCD is ↑ in those with an aborted cardiac arrest, recurrent syncope, and polymorphic/bidirectional VT despite optimal therapy.

Drugs

- Three per cent of SCDs are due to cocaine use which causes LVH, premature atheroma, and small-vessel disease.
- Anabolic steroids can affect lipoprotein concentrations, and cause thrombosis, vasospasm, and direct injury to the myocardium.

Commotio cordis

- A blow to the chest occurring on the T wave upstroke can cause VF. Post-mortem reveals chest bruising and a structurally normal heart.

Prevention of sudden cardiac death in athletes

Primary prevention

- The sudden death of an athlete is a tragic event, which is often highly publicized, particularly as athletes represent the healthiest individuals within society. Screening, as advocated by the ESC, enables early detection of underlying CVD, as well as enabling lifestyle modification and therapeutic intervention.
- A pre-participation screening programme comprising history, physical examination, and 12-lead ECG has been in practice in Italy for over 30 years. An 89% reduction in SCD was reported, primarily due to improved identification of cardiomyopathies through cessation of ongoing competitive physical activity. Most individuals at risk will not be identified from their history and examination alone, given that 80% are asymptomatic, with SCD often the first presentation of an underlying CV pathology.
- Use of ECG screening improves the detection of early electrical changes which precede phenotypic expression. In addition, the ECG is essential to detect electrical conditions such as LQTS, BrS, and WPW syndrome.
- Prompt referral of affected individuals and first-degree relatives to a cardiologist with a specialist interest in inherited cardiac conditions enables appropriate assessment and follow-up.

Secondary prevention

- Most cardiac arrests occur out of hospital, and therefore, emergency response measures are crucial. A combination of prompt CPR together with defibrillation, compared with CPR alone, has been shown to be most effective in terms of survival outcomes.
- PublicAEDs should be available where they may be suitably stored and cardiac arrest may arise (schools, stations, sport stadiums) or where access to defibrillation devices is unavailable (planes, trains, ships). This, however, does not prevent the 70% of cardiac arrests that occur in the home, which are frequently unwitnessed.

Differentiating physiological adaptation from cardiomyopathy

- The overlap between physiology and early pathology can make diagnosis difficult.
- The next section identifies aspects of the history, physical examination, and investigations that may point to pathology.

Hypertrophic cardiomyopathy

- The 'grey zone' between physiology and pathology occurs with a wall thickness of between 13 and 15mm. The majority of athletes have normal wall thickness, but 'grey zone' overlap can occur in black ♂ (up to 14mm), white ♂ (up to 12mm), and black ♀ (up to 13mm).
- The following may help to differentiate physiology from pathology:
    - Individuals may have symptoms (shortness of breath, palpitations, syncope, presyncope, and chest pain).
    - Up to 95% of individuals with HCM have an abnormal ECG (inferior and/or lateral TWI, large QRS voltages, Q waves, ST-segment depression, non-specific intraventricular delay (≥140ms), complete LBBB, LAE, LAD, and premature ventricular ectopics (PVEs).
    - The pattern of hypertrophy is usually asymmetrical, septal, or apical. There may also be elongation of the MV leaflets and anomalous insertion of the papillary muscles in individuals with HCM. It is important to note that whereas diastolic dysfunction is abnormal in sedentary individuals with HCM, it is usually normal in athletes with HCM.
    - Low peak VO_2 and NSVT on exercise testing.
    - NSVT/VT on Holter monitoring.
    - Myocardial crypts and LGE on MRI.
    - Positive family history/positive genetics.
    - In the absence of a family history, detraining for 3 months leading to regression of LVH may be more suggestive of physiological hypertrophy.

Arrhythmogenic cardiomyopathy

- Differentiation between physiological RV enlargement and anterior TWI from pathological dilatation and ECG changes is particularly difficult in endurance athletes who may demonstrate both changes.
- The following may help to differentiate physiology from pathology:
    - Individuals may have symptoms.
    - Up to 80% of individuals have an abnormal ECG (inferior and/or lateral TWI—LV predominance); TWI in the anterior leads—RV predominance; ST-segment depression; epsilon wave; RAD; PVEs).
    - Late potentials on signal-averaged ECG.
    - Abnormal echocardiographic parameters (dilatation accompanied by wall motion abnormalities or aneurysms).
    - NSVT/VT on Holter monitoring.
    - LGE on MRI.
    - Positive family history/positive genetics.

Dilated cardiomyopathy

- Fifteen per cent of elite ♂ athletes demonstrate LVEDV dimensions of >60mm, overlapping with pathological dilatation.
- The following may help to differentiate physiology from pathology:
  - Individuals may have symptoms.
  - Abnormal ECG (Q waves, ST-segment depression, TWI, non-specific intraventricular delay, complete LBBB, atrial enlargement, axis deviation, PVCs).
  - Low peak VO_2 and NSVT on exercise testing.
  - NSVT/VT on Holter monitoring.
  - LGE on MRI.
  - No improvement of LV function on exercise echocardiography.
  - Positive family history/positive genetics.

Left ventricular non-compaction

- Athletes frequently demonstrate trabeculations within the LV cavity; 8% of athletes may even fulfil criteria for LVNC.
- The following may help to differentiate physiology from pathology:
  - Individuals may have symptoms.
  - Abnormal ECG (ST-segment depression, inferolateral TWI, LBBB).
  - Abnormal echocardiographic parameters (↑ trabeculations).
  - Low peak VO_2 and NSVT on exercise testing.
  - NSVT/VT on Holter monitoring.
  - LGE on MRI.
  - Positive family history.

Cardiomyopathies: recommendations for sports participation

Required assessments

- Individuals with underlying cardiomyopathies should, as a minimum, undergo:
    - A full history, including assessment of symptomatic status
    - Physical examination
    - ECG
    - TTE
    - Exercise testing.
- Further investigations should be guided by the underlying pathology, including prolonged ECG monitoring, functional stress testing, and MRI. Athletes with an underlying pathology should be reassessed regularly.
- The following section addresses the exercise restrictions in those conditions most likely to be encountered in a clinical setting.

Recommendations

- The 2020 ESC recommendations for competitive sports in those with cardiomyopathies are listed in Table 19.2.[1]

Table 19.2 Recommendations for competitive sports participation in athletes with cardiomyopathies

Condition	Eligibility criteria	Recommendations
HCM (low risk)	No markers of ↑ risk: • Symptomatic or history of cardiac arrest or unexplained syncope • Moderate ESC risk score (>4%) at 5 years • LVOT gradient at rest >30mmHg • Abnormal BP response to exercise • Exercise-induced arrhythmias	Can engage in competitive sports (avoiding those where syncope may lead to harm/death) if no markers of ↑ risk
HCM genotype positive only	No phenotypic features of HCM	All competitive sports if phenotype negative
DCM (high risk)	Any of the following: • Symptomatic or history of cardiac arrest or unexplained syncope • LVEF <45% • Ventricular arrhythmias on exercise testing and Holter monitoring • Extensive LGE >20% • Evidence of high-risk genotype (lamin A/C, filamin C)	Competitive sports not recommended
DCM (low risk)	All of the following: • Asymptomatic • Mildly reduced EF (45–50%) • Ability to ↑ EF by 10–15% during exercise • No ventricular arrhythmias on exercise testing or Holter monitoring • Absence of LGE on CMR • No evidence of high-risk genotype (lamin A/C, filamin C)	Can engage in competitive sports (avoiding those where syncope may be associated with harm/death)

Table 19.2 (*Contd.*)

Condition	Eligibility criteria	Recommendations
DCM genotype positive only	No phenotypic features of DCM	All competitive sports if no evidence of high-risk genotype (lamin A/C, filamin C)
ACM		Advise not to engage in competitive sports and to limit to low-intensity recreational activities
ACM (low risk)	All of the following: • No history of cardiac arrest, ventricular arrhythmias, or unexplained syncope • Minimal structural abnormalities • <500 ectopics/24h • No ventricular arrhythmias on exercise testing or Holter monitoring	Moderate-intensity recreational activity may be considered
ACM genotype positive only	No phenotypic features of ACM	Advise not to engage in competitive sports
LVNC	LVEF ≥50% and no arrhythmias on exercise testing or Holter monitoring	Can engage in competitive sports (avoiding those where syncope may be associated with harm/death)
Myocarditis	Asymptomatic, normal LVEF, normal cardiac biomarkers, no arrhythmias on exercise testing or Holter monitoring	All competitive sports Restrict all athletes for at least 3–6 months

HCM, hypertrophic cardiomyopathy; ESC, European Society of Cardiology; LVOT, left ventricular outflow tract; BP, blood pressure; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; LGE, left gadolinium enhancement; EF, ejection fraction; CMR, cardiac magnetic resonance; ACM, arrhythmogenic cardiomyopathy; LVNC, left ventricular non-compaction.

Follow-up

- Annual follow-up is recommended for all individuals for assessment of phenotypic features.
- Six-monthly follow-up should be considered for adolescents and young adults who may be at higher risk of SCD, as well as for those with high-risk mutations. In DCM, these include lamin A/C and filamin C, and in those with ACM, *DSP*, *TMEM43*, or multiple pathogenic variants.
- In those with myocarditis, asymptomatic athletes with LGE should remain under annual clinical surveillance.

Reference

1. Pellicia A, Sharma S, Gati S, *et al*. 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease: the task force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;**42**:17–96.

Arrhythmias: recommendations for sports participation

Ventricular pre-excitation/Wolff–Parkinson–White syndrome

- WPW is a rare cause of SCD (up to 0.2% per year), and many individuals remain asymptomatic. However, individuals may develop symptomatic AV nodal tachycardia and are at risk of other arrhythmias such as AF which can degenerate into VF.
- Athletes are at ↑ risk of SCD if there is fast antegrade conduction. Therefore, an EP study and ablation should be performed in all symptomatic athletes with pre-excitation and documented arrhythmias.
- In asymptomatic athletes with pre-excitation, an EP study is recommended for risk stratification, with ablation performed in those with high-risk features. Asymptomatic low-risk athletes may participate in competitive sports.

Paroxysmal supraventricular tachycardia

- Paroxysmal SVT can lead to high HR and haemodynamic instability, even in the presence of a structurally normal heart. Therefore, ablation is recommended in athletes.
- If an athlete does not wish to undergo ablation, they may participate in competitive sports if the arrhythmia is infrequent, unrelated to exercise, and well tolerated, and syncope during participation would not result in harm/death.

Channelopathies

- General precautions should be employed. In the case of LQTS, avoidance of QT-prolonging medications, dehydration, and electrolyte imbalance. For BrS, avoidance of triggering drugs, dehydration, electrolyte imbalance, and hyperthermia.
- In patients with symptomatic LQTS or ↑ QTc on ECG, competitive sports should be avoided. In those who are genotype-positive but phenotype-negative, one should employ a shared decision-making approach.
- Competitive sports may be considered in athletes with BrS, those with an inducible Brugada pattern, and those who are genotype-positive and phenotype negative, if competitive sports likely to ↑ their core temperature are avoided.

Recommendations

- Recommendations for competitive sports in individuals with arrhythmias or pro-arrhythmic conditions are detailed in Table 19.3.[1]

Follow-up

- Annual follow-up should be considered for all conditions listed in Table 19.3. However, frequency should be dictated by symptoms and documentation of arrhythmias.
- For genotype-positive, phenotype-negative individuals, annual assessment for phenotypic features should be undertaken.

Table 19.3 Recommendations for competitive sports participation in athletes with arrhythmias or conditions predisposing to arrhythmias

Rhythm/underlying condition	Eligibility criteria	Recommendations
Pre-excitation and documented arrhythmias		All competitive sports 1 month post-ablation
Asymptomatic pre-excitation (not high risk)	If asymptomatic and EP study demonstrates low-risk features	All competitive sports
Asymptomatic pre-excitation (high risk)	Shortest pre-excited RR interval <250ms	All competitive sports 1 month post-ablation
Paroxysmal SVT (post-ablation)		All competitive sports 1 month post-ablation
Paroxysmal SVT (no ablation)		Can engage in competitive sports (avoiding those where syncope may be associated with harm/death)
AF (AF well tolerated, no antiarrhythmics)	No underlying structural heart disease, good rate control during exercise	All sports No contact sports if on anticoagulation
AF (recurrent, symptomatic and/no wish to take antiarrhythmics)	Post-ablation	1 month post-ablation* No contact sports if on anticoagulation
Atrial flutter	Post-ablation	1 month post-ablation* No contact sports if on anticoagulation
LQTS	Prior cardiac arrest, arrhythmic syncope. Even when on β-blockers, QTc >500ms, genotype positive, and QTc ≥470ms in men and ≥480ms in women	No competitive sports
LQTS genotype positive only	QTc normal	Shared decision-making
BrS	Asymptomatic	All competitive sports, with the exception of those associated with ↑ core temperature to 39°C
Brugada genotype positive only	No phenotypic features of Brugada syndrome	All competitive sports, with the exception of those associated with ↑ core temperature to 39°C
CPVT		No competitive sports

* It is unknown whether continuation of sports after ablation can lead to disease progression or to recurrence of atrial fibrillation, and therefore, no recommendation on 'safe dose' of sports post-ablation can be made.

EP, electrophysiology; SVT, supraventricular tachycardia; AF, atrial fibrillation; LQTS, long QT syndrome; BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia.

Reference

1. Pellicia A, Sharma S, Gati S, *et al*. 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease: the task force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;**42**:17–96.

Ischaemic heart disease: recommendations for sports participation

- IHD is the most common cause of SCD during exercise in those aged >35 years. This is thought to be caused by plaque rupture or high-intensity exercise exceeding the threshold of ischaemia.
- Physical inactivity is a risk factor for CAD, and therefore, it is essential to provide appropriate recommendations to athletes with IHD.
- The first step in the assessment of an athlete is to calculate their risk score. Established risk scores, such as SCORE-2 risk charts, may be used (see ➔ Risk assessment tools, p. 10).

Investigations

- If an athlete has low CV risk (no CVD risk factors), no further investigations are required and they may participate in competitive sports.
- Athletes who are at high risk and wish to take part in high- or very high-intensity sports should undergo a full medical history, physical examination, ECG, and exercise stress testing.
- Functional imaging or CTCA should also be considered in asymptomatic athletes who are high or very high risk.
- If there is evidence of high-risk features on exercise testing/functional imaging or CTCA is positive, then athletes should undergo invasive coronary angiography.

Management

- Individuals with significant CAD should undergo PCI. In the case of those with non-significant CAD, as long as they are low risk, then they should be advised that they may participate in competitive sports; however, restrictions may apply to those sports with highest CV demand. In those with high-risk features, competitive sports are not advised.
- Individuals who undergo PCI may be risk-stratified at 3 months and, if low risk, may compete in most competitive sports, with the exception of those with high CV demand. High-risk individuals should not participate in competitive sports.

Recommendations

- Recommendations for competitive sports in individuals with IHD are listed in Table 19.4 and Fig. 19.8.[1]
- Annual follow-up should be undertaken in athletes with IHD.

Table 19.4 Summary of ESC recommendations for competitive sports participation in athletes with ischaemic heart disease

Condition	Eligibility criteria	Recommendations
IHD and high risk of cardiac events	Any of the following: • Symptoms • LV function <50% • Ischaemia on exercise • Arrhythmias on exercise • >50% stenosis of left main stem • >70% of major coronary arteries	No competitive sports
IHD and low risk of cardiac events	No high-risk features	Most competitive sports. However, restriction limited to sports with highest cardiovascular demands

IHD, ischaemic heart disease; LV, left ventricular.

Reference

1. Borjesson M, Dellborg M, Niebauer JR, *et al*. Recommendations for participation in leisure time or competitive sports in athletes-patients with coronary artery disease: a position statement from the Sports Cardiology Section of the European Association of Preventive Cardiology (EAPC). *Eur Heart J*. 2019;**40**:13–18.

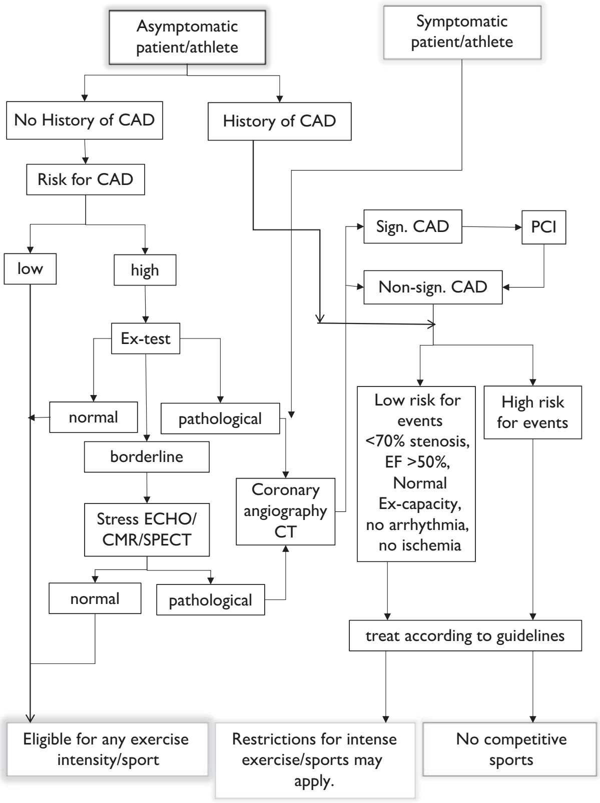
Asymptomatic patient/athlete
Symptomatic patient/athlete
No History of CAD
History of CAD
Risk for CAD
Sign. CAD
PCI
low
high
Non-sign. CAD
Ex-test
normal
pathological
Low risk for events <70% stenosis, EF >50%, Normal Ex-capacity, no arrhythmia, no ischemia
High risk for events
borderline
Coronary angiography CT
Stress ECHO/ CMR/SPECT
normal
pathological
treat according to guidelines
Eligible for any exercise intensity/sport
Restrictions for intense exercise/sports may apply.
No competitive sports

Fig. 19.8 Recommendations for assessment of asymptomatic and symptomatic athletes with, or at risk of, coronary artery disease. CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; ECHO, echocardiography; ETT, exercise tolerance test; PCI, percutaneous intervention; SPECT, single photon emission computed tomography.

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Hypertension: recommendations for sports participation

- Athletes with hypertension should be treated in accordance with existing guidelines. Low, moderate, high, and very high risk equate to a 10-year risk of CV mortality of <1%, 1–4%, 5–10%, and >10%, respectively.
- In athletes with low to moderate CV risk, no restrictions apply.
- In athletes with high or very high risk in whom BP control is achieved, competitive sports participation is allowed (except for those with high static components). If BP is not well controlled, temporary restriction from competitive sports is recommended.
- Recommendations for competitive sports participation in athletes with hypertension are listed in Table 19.5.[1]

Table 19.5 Summary of ESC recommendations for competitive sports participation in athletes with coronary artery disease

Eligibility criteria	Recommendations	Follow-up
BP well controlled No other RF No TOD No ACC	Can engage in competitive sports	Annually
BP well controlled RF well controlled No TOD No ACC	Can engage in competitive sports	6- to 12-monthly
BP well controlled RF well controlled TOD present No ACC	Can engage in competitive sports, apart from those with a high dynamic component (e.g. power sports)	6-monthly
BP well controlled RF well controlled TOD not present/present ACC present	Can engage in competitive sports, apart from those with a high dynamic component (e.g. power sports)	6-monthly

BP, blood pressure; RF, risk factors; TOD, target organ damage; ACC, associated clinical condition.

Target organ damage includes left ventricular hypertrophy, ultrasound confirmation of plaque or arterial wall thickening, microalbuminuria, and ↑ creatinine level.

Clinical conditions include retinopathy, cerebrovascular disease, heart failure, ischaemic heart disease, impaired renal function, proteinuria, and peripheral vascular disease.

Adapted from Niebauer J *et al*. *Eur Heart J*. 2018;**39**(40):3664–71, with permission from the ESC. Copyright © The European Society of Cardiology 2018.

Reference

1. Niebauer J, Borjesson M, Carre F, *et al*. Recommendations for participation in competitive sports of athletes with arterial hypertension: a position statement from the sports cardiology section of the European Association of Preventive Cardiology (EAPC). *Eur Heart J*. 2018;**39**:3664–71.

Valvular heart disease: recommendations for sports participation

- Recommendations for competitive sports in individuals with VHD are listed in Table 19.6.[1]
- Multivalvular diseases should be managed as per the predominant lesion, and post-valvuloplasty lesions should be managed as per the degree of residual stenosis and/or regurgitation.

Table 19.6 Recommendations for competitive sports participation in athletes with valvular heart disease

Valvular lesion	Eligibility criteria	Recommendations	Follow-up
Mitral valve stenosis (MS)	Mild MS with resting PASP <40mmHg and normal exercise stress test	All competitive sports	Annually
	Moderate MS with resting PASP <40mmHg and normal exercise stress test	Low-intensity competitive sports	Annually
	Severe MS	No competitive sports	6-monthly
Mitral valve regurgitation (MR)	Mild MR	All competitive sports	Annually
	Moderate MR, LVEDD <60mm, LVEF ≥60%, resting PASP <50mmHg, normal exercise stress test	All competitive sports	Annually
	Severe MR, LVEDD <60mm, LVEF ≥60%, resting PASP <50mmHg, normal exercise stress test	Low-intensity competitive sports	6-monthly
Aortic valve stenosis (AS)	Mild AS	All competitive sports	Annually
	Moderate AS, LVEF ≥50%, good functional capacity and normal BP response during exercise	Low- to moderate-intensity competitive sports	Annually
	Severe AS with LVEF >50%	Low-intensity skill sports	6-monthly
Aortic regurgitation (AR)	Mild AR	All competitive sports	Annually
	Moderate AR, non-dilated LV, LVEF >50%, normal exercise stress test	All competitive sports	Annually
	Severe AR, mild to moderately dilated LV, LVEF >50%, normal exercise stress test	Low- to moderate-intensity competitive sports	6-monthly

Table 19.6 (*Contd.*)

Valvular lesion	Eligibility criteria	Recommendations	Follow-up
Mitral valve prolapse (MVP)	Mild/moderate MR, asymptomatic with no inferior TWI, ectopics arising from the LV, inferobasal myocardial fibrosis	All competitive sports	Annually
	Severe MR, asymptomatic with no inferior TWI, ectopics arising from the LV, inferobasal myocardial fibrosis, LVEDD <60mm, LVEF ≥60%, resting PASP <50mmHg, normal exercise stress test	Low- to moderate-intensity competitive sports	6-monthly

Reference

1. Pellicia A, Sharma S, Gati S, *et al*. 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease: the task force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;**42**:17–96.

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